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Blood, Sweat and Tears:
A Case Study of the Development of Cultured Red Blood Cells for Transfusion

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ABSTRACT

This thesis is an in-depth case study of an interdisciplinary, paradigm breaking, research team who are seeking to develop cultured red blood cells (RBCs) for transfusion using stem cells (known as the BloodPharma project). It answers the research question: *What can an in-depth case study of the BloodPharma project reveal about everyday scientific practice and the project management of a large research programme?* The BloodPharma project occupies a unique position within the stem cell arena due to the size and multi-disciplinary nature of the project team, and the unique risk profile of cultured RBCs. The historical significance of blood donation is combined with the modern innovation of stem cell usage, to create a product which is both novel but also highly emotive.

The case study comprises interviews with a range of stakeholders, laboratory observation, and participant observation of public outreach activities. In addition presence at team meetings and teleconferences has allowed an in-depth analysis of the project progression. The thesis has also drawn heavily on science and technology studies and scientific literature, as well as on information gathered from a wide variety of conferences and workshops.

Key findings indicate that early stage laboratory work in this interdisciplinary project is achieved through the standardisation of work across different research spaces, with training and visual aids used to overcome the hurdle of tacit knowledge associated with the development of stem cell technologies. In designing early stage laboratory work the team looked to the human body as a benchmark of *in vivo* RBC production, using *in vivo* cells as a dual standard for which the team must aim, but cannot fall short of. Scale-up and standardisation were identified as the key challenges to the translation of this early stage laboratory work into a clinically useable product. These challenges require new expertise and innovation, and are an example of the translational obstacles of tacit knowledge and visual techniques which are found in the wider stem cell field. The use of target markets was identified by the team as a stepping stone to larger scale production, although in common with other stem cell

therapies the clinical trials route to first-in-human use is still unclear. The uncertainty of regulation for stem cell products, and specifically how this relates to the BloodPharma project, is also a key finding of this thesis. Interactions with the regulatory system are seen as a necessity but also represent an area of confusion for laboratory researchers, requiring much specialist knowledge to understand and navigate regulatory documents. Regulatory expertise is brought to the BloodPharma project through reliance on particular members of staff. Public outreach has formed an important part of the BloodPharma project and shows the scientists stepping outside their primary area of expertise, a reflection of the broader trend amongst academic research to demonstrate 'broader impact criteria'. Public outreach for the BloodPharma team was found to occupy a unique niche, given that the team must balance the promotion of a future product with the preservation of the current donation system.

This research is of a case study which goes beyond the boundaries of the laboratory, to look not only at early stage laboratory work, but also at the way in which the team envisions future translation and regulatory hurdles, and the public outreach which must combine to develop a novel stem cell therapy. The thesis is the first in-depth case study to follow a large, interdisciplinary, stem cell team through the work they carry out both within the laboratory space, and outside it; challenging the idea of what it means to carry out scientific work in this novel area of stem cell therapies.

DECLARATION OF OWN WORK

This is to certify that the work contained within has been composed by me and is entirely my own work. No part of this thesis has been submitted for any other degree or professional qualification.

Signed:

Date:

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ACRONYMS

BME	Black and Minority Ethnic
CJD	Creutzfeldt-Jakob Disease
DARPA	(USA) Defence Advanced Research Projects Agency
DH	Department of Health
EUTCD	European Union Tissues and Cells Directive
GMP	Good Manufacturing Practice
GTAC	Gene Therapy Advisory Committee
HBOCs	Haemoglobin-Based Oxygen Carriers
hESCs	Human Embryonic Stem Cells
HO	Home Office
HSE	Health and Safety Executive
HTA	Human Tissue Authority
iPSC	Induced Pluripotent Stem Cell
MHRA	Medicine and Healthcare Products Regulatory Agency
MRC	Medical Research Council
NHSBT	National Health Service Blood and Transplant Authority
NREC	National Research Ethics Committee
RBC	Red Blood Cell
SaBTO	Advisory Committee on the Safety of Blood, Tissues and Organs
SC	Stem Cell
SNBTS	Scottish National Blood Transfusion Service
SOP	Standard Operating Procedure
TTIs	Transfusion-Transmissible Infections
UKSCB	UK Stem Cell Bank
WHO	World Health Organisation

IDENTIFICATION OF QUOTATIONS

To preserve anonymity codes have been used to identify the main research expertise of interviewees. More information about interview recruitment is included in Chapter Two.

The prefixes:

CS	Case Study (BloodPharma project)
O	Other
R	Regulatory

are followed by the identification of the area of expertise:

Lab	Laboratory
Reg	Regulatory
Clin	Clinical
Ind	Industry
Other	Other

For example (CS/Lab) would identify a respondent who worked in the laboratory for the BloodPharma project.

CHAPTER 1: INTRODUCTION

INTRODUCTION

This thesis is an in-depth case study of a paradigm breaking, multi-sited, interdisciplinary research team carrying out innovation in an area of high uncertainty, where control over biological processes, team-work, regulatory and public interest issues are intrinsically connected with the laboratory science. It is a case study of a team of scientists who are carrying out laboratory work which has the potential for new product development, but whose work also takes them outside the laboratory. The key research question of the thesis is: **What can an in-depth case study of the BloodPharma project reveal about everyday scientific practice and the project management of a large research programme?**

Many years of investment in basic stem cell research has yet to yield more than a small number of clinical therapies. As such the innovation and regulatory pathways (for example the clinical trials template) are still uncertain, and concrete examples of everyday innovation practices are lacking. An in-depth case study of a particular case, in this instance the BloodPharma project, will contribute to an understanding of the hurdles and challenges faced by a research team. This thesis will analyse the practices of this visionary research team as it seeks to develop a stem cell therapy from basic research to clinical use, providing an in-depth case study of a real team and the implications for its everyday actions.

The case study for this thesis is a multi-centre, interdisciplinary, collaborative team that is undertaking a scientific research project to develop cultured red blood cells (RBCs) from stem cells, known as the BloodPharma project. RBC transfusions in the UK are currently obtained from altruistic donors, however supply is limited and there is an ongoing risk of infection transmission. Previous attempts to create alternative blood sources have mostly been unsuccessful and there is currently no clinical substitute for RBCs. In 2009 the BloodPharma project was awarded £3million funding by the Wellcome Trust to develop an alternative method of blood production. If successful the technology will allow an unlimited number of RBCs to

be produced, free of infection and of a blood type suitable for the majority of the recipient population. It is hoped that cultured RBCs may negate the need for human blood donation, or provide an enhanced treatment for patients with certain blood disorders.

Blood transfusion as a medical technique in its current form has been practised for around 100 years and has become a vital component of modern medicine. It is therefore necessary to situate the new technique of culturing RBCs as both a continuation and reformation of a widely used and accepted practice. This case study is about the important period of transition from an existing, well used and publicly accepted technology to a new technology that may have huge consequences. It is also the story of a team seeking to develop a clinical stem cell therapy in the face of uncertainty about future scale-up and regulation. Blood is currently donated altruistically and tested, processed, fractionated and supplied to those who need it. In the future blood may be a stem cell product that reduces reliance on blood donors and supplies a continuous source of safe, standardised blood that is cultured in the laboratory. Cultured RBCs could potentially lead to a revolutionary change in the way that blood is produced, stored and distributed, as well as bringing additional benefits to patients. Currently these cultured cells are produced from stem cells, a technique which could also have a disruptive effect on public attitudes towards future blood transfusion technologies.

The empirical data for this thesis have been gathered over three years and comprise interview, laboratory observation and participant observation data. I have been allowed access to all stages of the project and this thesis brings insight into the world of clinical stem cell therapy development. The BloodPharma project represents a unique example in the wider arena of stem cell therapy development. The team is attempting to replace a product which already has an accepted alternative in conventional blood donation. This gives the team a benchmark for their work, and also a regulatory hurdle in having to justify the replacement of an established practice. The project comprises teams in multiple laboratories across the UK and Ireland. The structure of the team is therefore unusual, for example there are six

principal investigators named on the project grant. Finally, unlike other stem cell therapies, which are designed for small numbers of recipients or which use relatively small numbers of cells, the BloodPharma project must anticipate an enormous challenge of production and scale-up. Each unit of blood requires around two trillion RBCs, and the UK alone uses two million units of blood a year.

The Key Research Questions

This thesis provides an analysis of the Project team as it navigates the early stage development of the cultured blood product, and is driven by five key research questions. These will be explained in more detail along with the sub-questions identified.

1. **How is early stage laboratory work achieved through interdisciplinary, multi-lab working, where standardisation of methods is difficult and where there exists an accepted technology?**

The BloodPharma team is spread across different laboratories within the UK and Ireland, and with a mix of primary disciplines within the team. This question seeks to explore how these smaller teams co-ordinate the production of a novel therapy. By their very nature stem cells can form different tissues types and control is difficult. Tacit knowledge and expertise is therefore a vital part of standardising work across different laboratory spaces. The BloodPharma team has an existing product in the form of donated blood, which acts as a benchmark for early stage laboratory work.

- *What are the challenges of working across multiple sites and different disciplinary areas?*
- *How important is tacit knowledge in early stage laboratory practices?*
- *What role does a natural/synthetic distinction play and how does the team use the human body as an exemplar?*
- *To what extent does the team envision future product development pathways at an early stage of the research?*

2. **What does the Team see as the key challenges associated with translating cultured blood into a viable clinical product and how do these shape everyday practices?**

The scale-up and automation associated with the BloodPharma project makes this a unique case amongst stem cell derived products. Uncertainties exist in the potential clinical trial regime for stem cell products, which can impact on the ability of researchers to forward plan. Nevertheless suitable target populations have had to be identified and uses imagined beyond the production of the initial product.

- *What are the particular challenges of scale-up and automation within the BloodPharma Project?*
- *How do uncertainties in the clinical trial regime for stem cells impact on the planning of potential trials for the BloodPharma product?*
- *What are the markets for this product and to what extent does the team think beyond this initial product goal?*

3. **How does the regulatory system, and perceptions of risk, shape the activities of the BloodPharma team and the development of the cultured blood product, and what can this case study tell us more generally about the regulatory system for stem cell products?**

The regulatory system for stem cell research in the UK is complex and has been built on previous legislation designed in the wake of particular historical events. The BloodPharma team must navigate this system which requires its own particular set of knowledge and expertise. The BloodPharma product will bring specific risks, which will impact on how it is perceived by the regulators, and on the specific hurdles which the team must overcome. Studying this example will provide more information about how the regulatory system for stem cells is working in practice across the wider regenerative medicine arena.

- *What can the history of regulation for stem cells tell us about the regulation of the BloodPharma product?*
- *How does the BloodPharma team navigate the regulatory system, and what particular knowledge and expertise does it have to acquire?*
- *How do the anticipated risks associated with this cultured blood product impact on the team's perception of regulatory requirements?*

4. **What are the main drivers and motivators behind the BloodPharma team engaging with public outreach, and how do the scientists respond to their own role as public communicators?**

Public communication is becoming an integral part of the modern day research community and a requirement of many funding awards. For many basic laboratory scientists this represents a new area of expertise with which they must engage. The BloodPharma project brings with it unique challenges to downstream engagement, whilst also balancing the current needs of the Blood Transfusion Services.

- *What expectations do the team have in undertaking public outreach and what are the different reasons for them performing this activity?*
- *What specific activities were carried out and how did the results of these impact on the team's thinking about its product?*
- *How do the scientists experience their own role as public communicators?*
- *What are the specific challenges for up-stream engagement in this project?*

The rest of this chapter will provide a background to the work of the BloodPharma team, situating it within the context of current clinical usage of donor blood transfusion. It will provide an overview of the historical development of blood donation and will show that the current practice of blood transfusion has changed little since the method entered everyday clinical usage. A synopsis of each chapter will then be provided.

SITUATING THE BLOODPHARMA PROJECT WITHIN THE HISTORICAL CONTEXT OF DONOR BLOOD TRANSFUSION

Blood has been revered for thousands of years and has come over the last century to be associated with the practice of human blood donation and transfusion. The BloodPharma project, if successful, has the ability to change society's relationship with human blood in the space of a decade. In fifty years time it may seem inconceivable that our medical system once relied on human donors to supply such a vital product. Blood has often been attributed cultural and symbolic significance, as is the colour red with which blood is often associated. Greek mythology tells of the red rose growing from the blood of Adonis, whilst the Christian religion brought

with it a strong association with blood as a 'life-giving force'. Conversely stories of vampires portray creatures who seek to drain the blood of humans. On a couple of occasions I have heard clinicians talk of phlebotomists as 'vampires', in the context of calculating how much blood would be required from critically ill patients undergoing tests. In more modern times the colour red has been associated with the ribbons worn in support of HIV/AIDS victims.

The practice of draining blood from a patient, bloodletting, was first recorded in 430BC and remained a common practice until the nineteenth century (Giangrande, 2000). Bloodletting was considered to relieve many conditions, including fevers, back pain, madness, headaches, hypertension and 'going into decline' (Starr, 1999, pg.17). Although bloodletting was carried out by skilled professionals a greater knowledge of the vascular system was required for blood transfusions. The publication of William Harvey's book 'De Motu Cordis' ('On the motion of the heart and blood') in 1628 represented a step forward in the understanding of the circulatory system, and led to the first transfusion experiments. It is generally accepted that Richard Lower carried out the first transfusion from animal to animal in 1665, which appears to mark the beginning of a trend in transfusion experiments (Brown, 1948). Thomas Coxe's (1666-1667) paper describes his experiment to bleed a mangy dog into a healthy dog. The result being no difference in the healthy dog but the mangy dog was cured within two weeks (apparently due to being drained of '14 or 16 ounces' of blood). Coxe writes that the considerable loss of blood the dog underwent was "perhaps the quickest and surest remedy for the cure of that sort of disease, he was infected with, both in man and beast" (Coxe, 1666-1667, pg.3).

Although this experiment demonstrated the transfer of blood from one animal to another its outcome appears to focus on supporting the long held idea that blood loss could affect a cure, showing that the old views on bloodletting would take time to be abandoned. It was also widely accepted that characteristics were contained within the blood; so many experiments took place transfusing the blood of docile animals (such as lambs) into humans, with the hope of curing madness (Brown, 1948). In many cases this appeared to succeed, probably because the subsequent shock reaction left

the patients too ill to move. Jean Denis published a series of pamphlets giving details of experiments in which the blood of lambs cured lethargy and fever. Unfortunately at the end of 1667 it transpired that one of the men mentioned in Denis' accounts had subsequently died as a result of the transfusion experiment, and the public outcry effectively put a stop to this fledgling technology for the next 100 years (Brown, 1948, pg.7). Denis was eventually exonerated of any wrongdoing, reports suggesting that the patient's wife had found his recovery rather irritating and so poisoned him.

The start of modern transfusion medicine is credited to James Blundell in 1818, who recognised the need to transfuse humans only with human blood. It was not, however, until the work of Karl Landsteiner in 1901 that the first published results of blood types were made (Landsteiner, 1901) and routine blood typing was not practised until the 1920's (with the Rhesus positive and negative blood identified in 1941) (Landsteiner and Wiener, 1941). Without anticoagulants transfusion of large quantities of blood was difficult and early techniques relied on connecting the vein of the donor to the artery of the recipient or stirring the blood to prevent clotting. Richard Lewinsohn is accredited with first introducing sodium citrate to medical transfusions in 1915 (Giangrande, 2000), and citrate-phosphate-dextrose is now the normal anticoagulant used for long term blood storage. In 1921 the first blood bank was set up in London by Percy Oliver, after the branch of the Red Cross for which he was secretary received a call for blood donors. He had the idea of setting up a list of donors who could be called upon at short notice, as anticoagulant use was not widespread so donors were required to attend the hospital and often be in the same room as the recipient. (Giangrande, 2000). In 1937 Bernard Fantus set up the blood bank as we now know it, with blood refrigerated for up to ten days.

Other donation centres sprung up but most of these paid donors for their blood, a donation model which spread across most of the world. The Second World War provided the catalyst for many improvements in the collection, storage and transportation of blood (Edwards and Davie, 1940), with the British army abandoning the practice of extracting blood from soldiers at the front and instead supplying fighting units with stored blood transfusions. It was also around this time

that work started on obtaining products from fractionated blood, such as albumin, used to treat burns victims, and immunoglobulins used to treat infectious diseases. The war provided not just the need for such products but also the urgency that allowed many experimental products to be used without being rigorously tested. Although some adverse effects were reported it is likely this saved many lives, with one such product developed being factor VIII, which became vital in the treatment of haemophilia.

Today blood is one of medicines' 'most vital commodities' with a price many hundred times that of crude oil (Starr, 1999, pg.x). It is used in many forms, from whole blood transfusions to direct infusion of RBCs, white blood cells, antibodies, clotting factors, and plasma. Blood transfusions allow surgeons to overcome the inevitable blood loss during surgery and blood fractionation products are used to treat a range of blood based diseases such as haemophilia (Schneider, 2003). Many surgical techniques, such as open heart surgery, require large amounts of blood and could not have been developed without a reliable blood supply. The modern day process for blood collection and distribution is an extremely streamlined and efficient process, with donor and recipient safety the priority. Despite improvements in machinery, testing techniques, and storage times the basic process of transfusion remains the same, with blood collected from donors, processed, stored and then transfused to the recipient. Preventing the spread of transmissible diseases (often known as Transfusion-Transmissible Infections, TTIs) from donor to recipient is a priority and the UK system operates a self-selection policy, ensuring many unsuitable donors do not present themselves at a donation centre. If a donor is considered suitable they will donate a unit of whole blood[1] (about 470ml, roughly the same as the old 'pint' of blood). After donation the blood is processed, with whole blood donations being separated into their constituent parts. RBCs are subsequently tested for blood type and infection and are then packaged and stored for use. Whole

[1] There is also the option for donors to give component donations, although the vast majority of donations collected in the UK are still of whole blood. These component donors are connected to machines similar to a kidney dialysis machine. Components (plasma, platelets, red cells or white cells) are removed as needed and the remainder of the blood is retuned to the body.

blood transfusions are very rare in the UK, with most 'blood' transfusions being composed of red cells re-suspended in a carrying liquid.

For the purposes of this study donated blood technology is seen as the conventional and established technology, well defined, familiar and publicly acceptable. However blood transfusion could still be considered a technology in its infancy. Documented evidence has shown bloodletting to have been practised for almost two millennia, whilst a working knowledge of the human vascular system is barely 400 years old. The 'established' technology of clinical blood transfusion has actually been developed during living memory, although knowledge has advanced rapidly during this time. In less than 100 years it has moved from a very basic knowledge of blood typing to a system supplying millions of units every year, and blood transfusion has become publicly acceptable, with donors developing great attachment to the altruistic donation model employed in the UK. The current transfusion technology presented here may yet be replaced with the anticipated technology of cultured RBCs, negating the need for the vast majority of blood donors. The need for an alternative blood donation source is now more pressing, as the transfusion services are approaching a crisis point in their ability to provide the huge amount of blood required in current clinical practice. For example the SNBTS 2008 consultation (NHS, 2008) stated "*[The] SNBTS currently has a shortfall of 16,000 active blood donors required to support the current targets for blood collection, resulting in an increasing reliance on existing donors coming more frequently*".

The UK has an established and effective blood donation system but there are still challenges, both to the UK blood transfusion services and in the rest of the world, which highlight the need for the new cultured blood product being developed by the BloodPharma team. Contamination of donated blood with transferable diseases is one of the biggest hurdles to be faced by the blood transfusion services. The transfer of hepatitis from donor to recipient was an ongoing problem for many years (Starr, 1999, pg.216), however more widely publicised was the HIV contamination of plasma products, which was first recognised in the early 1980's and affected many haemophiliacs (Starr, 1999, pg.262). The authorities were slow to inform patients or

withdraw infected batches, which Starr (1999, pg.130) attributes to the reverence given to blood and its symbolic nature as a social gift, rather than a pharmaceutical product. In 2011 the public hearings for the Penrose Inquiry took place in Edinburgh. The Penrose Inquiry is the 'Scottish Public Inquiry into Hepatitis C/HIV acquired infection from NHS treatment in Scotland with blood and blood products' (The Penrose Inquiry, 2010). The inquiry sought to investigate the systems in place for collecting, testing and processing blood and blood products in Scotland, and for informing patients of possible contaminations. A large amount of blood testing is currently required to prevent future outbreaks of transmissible infections. Even in established blood donation systems the price of blood continues to rise as more extensive testing is implemented, at America's Blood Centres the price of a unit trebled between 1994 and 2004 (Ferguson, Prowse et al., 2008).

Acquiring adequate donors is another major hurdle faced by the transfusion services, with donor numbers falling and the UK transfusion services appearing to be heading towards a recruitment crisis. Currently only 4% of the UK population are registered blood donors (National Health Service, n.d). The Scottish National Blood Transfusion Service expressed a need to raise the donor levels from 175,000 in 2008 to 210,000 in 2010, in order to safeguard the transfusion service (NHS, 2008). Fluctuations in donor numbers do occur throughout the year and these fall into two categories - those that can be prepared for (such as the drop in donors during the summer and around Christmas) which to some extent can be minimised by donor campaigns, and those that cannot be avoided, such as a major flu outbreak. Various proposals have been made in an attempt to raise donor numbers, with donor recruitment campaigns often used in an effort to overcome the donor shortage. Members of the Scottish Government have also called for workers to be given paid leave in order to donate blood (Unknown, 2010). Currently there is a lifetime ban on donation for men who have sex with men, a situation that is likely to change in the near future, with studies showing that in Australia changing the deferral time from 5 years to 1 year after male-to-male sexual intercourse did not result in an increase in HIV in blood donations (Seed, Kiely et al., 2010). In recent years there has been debate over the accuracy of the haemoglobin finger-prick tests that are used to

determine if a donor has an acceptable haemoglobin level. Some researchers argue that the haemoglobin in the peripheral blood is not an accurate representation of the levels present in the venous blood (Morris, Ruel et al., 1999; Radtke, Polat et al., 2005). The SNBTS Consultation Document of 2008 states that implementation of new safety guidelines raising the acceptable haemoglobin count resulted in a loss of 10,000 donors per year (NHS, 2008).

Patients with certain blood conditions, including sickle cell anaemia and thalassemia require regular blood transfusions (Wayne, Kevy et al., 1993) and represent a different type of challenge to the blood transfusion system. Regularly transfused patients need blood that is a well matched as possible to the patient's blood type, in order to prevent immune rejection (Cox, Steane et al., 1988). Finding such blood can be challenging, as sickle cell anaemia is prevalent in groups from sub-Saharan Africa, India and the Middle East (Aidoo, Terlouw et al., 2002) and thalassemia from Mediterranean areas (Al-Awamy, 2000). The highest chance of matching blood correctly comes from donors with a similar genetic background, yet such donors are not only a minority in the UK population but are underrepresented in the UK transfusion services, both on blood, cord blood, and organ donation registers (NHS Blood and Transplant, 2010). The website of the UK Blood Transfusion Service (www.blood.co.uk) specifically appeals for blood donors from Black and Minority Ethnic groups (BME). The potential impact of the BloodPharma cultured blood on such user groups is discussed further in Chapter Four.

A number of innovations have been proposed to overcome the dual challenges of donor recruitment and possible infection risk. Few of these potential solutions have made it into mainstream medical practice and there still remain hurdles to overcome. There have been previous developments in the blood products industry, such as the use of recombinant DNA technology to provide Factor VIII, which show that an appropriate alternative technology can quickly become assimilated into mainstream practice. Therefore one focus has been on alternative methods that may replace, or lessen the need for, products acquired from conventional blood donations. These include temporary oxygen carriers (either based on processed haemoglobin or using

perflurocarbons), growth factors, clotting agents, thrombolysis inhibitors (which prevent the breakdown of blood clots), and autologous donation (through cell salvage or pre-operative donation) (Ferguson et al., 2008). Epoetin is also used to boost the RBC count of patients before surgery (Martyn, Farmer et al., 2002). Haemoglobin-Based Oxygen Carriers (HBOCs), derived from human or animal blood (Silverman, Weiskopf et al., 2009) and Perfluorocarbons (PFCs), which are synthetic oxygen carriers (Cohn and Cushing, 2009), were heralded as an alternative to RBC transfusion. Unfortunately neither product performed well in clinical trials and are not licensed for use in the UK or USA, although Hemopure is licensed for use in South Africa (Henkel-Honke and Oleck, 2007; Grethlein and Rajan, 2012).

These alternative methods of replacing blood have other drawbacks; one is that agents such as haemoglobin-based oxygen carriers still require donated blood and the second is a more social issue that the public perceive the use of 'blood substitutes' to be more risky. Ferguson et al. (2008) found that the public viewed blood substitutes as a 'substandard replacement' for actual blood, an unnatural and synthetic alternative, although the writers argue that this view may be changed by a more effective 'marketing' of alternative blood products. Other research on blood and blood substitutes has identified a greater acceptability of blood substitutes amongst medical professionals, when compared to journalists or blood donors (Lowe, Farrell et al., 2001). There was also a marked difference between the risk levels perceived by these groups concerning the infection rates through donation.

The historical significance of blood donation and the present challenges facing the supply of donated blood have been discussed here, so that the BloodPharma project can be viewed within the context of the wider blood transfusion field. The BloodPharma project was originally set up in response to a funding call from the American Defence Advanced Research Projects Agency *(*DARPA*)*, which was seeking to develop a method of producing blood in battlefield situations. The British team was not successful but realised that the expertise available would allow it to carry out the proposed project in the UK, which was then developed into the Wellcome Trust funded BloodPharma project. The project is a collaboration between

a variety of research teams and centres, including Roslin Cells, The Universities of Edinburgh and Glasgow, the Scottish National Blood Transfusion Service (SNBTS), the Medical Research Council (MRC) Centre for Regenerative Medicine, NHS Blood and Transplant, and the Irish Transfusion Service. The researchers are based at various locations around Edinburgh, as well as in Glasgow, Bristol and Dublin, and more recently Dundee. This collaborative approach makes the BloodPharma project an interesting study of not just how research is carried out within one scientific team, but how different teams collaborate to overcome the challenges associated with working across multiple research spaces. The BloodPharma project is officially titled 'Proof of principle: human embryonic stem cell derived red cell concentrates for clinical transfusion'. The project goal is to develop a technology that will allow RBCs to be cultured in the laboratory, eventually providing a limitless and infection free source of blood for transfusion. The project was awarded £2.9million by the Wellcome Trust between 2009 and 2012, with an additional injection of £2.5million from the Scottish Funding Council, from 2011-2016. It is hoped that by the time the project finishes it will be possible to generate small quantities of blood that may be suitable for initial animal and human safety tests.

Objectives of the BloodPharma Project

The project brings together three research components, the generation of embryonic stem cells to good manufacturing practice (GMP) standards, the generation of blood (haematopoietic) stem cells and the generation of RBCs from human haematopoietic stem cells (Mountford, 2008). Each of these three individual components have been generated previously to research grade but the Wellcome Trust Funding will allow further research to combine these three areas - deriving human embryonic stem cells, driving them to produce haematopoietic stem cells and finally scaling up and producing RBCs. These cells will also have to be derived at clinical level, which means meeting requirements for scale, quality and safety to allow initial clinical trials to proceed. The goal of this work over a longer time span is to produce O negative RBCs, the universal donor. For this to be achieved an O negative stem cell line would be required. Initial work on any blood group is possible but would restrict the blood types into which this cultured blood could be safely transfused.

The overall goals of the BloodPharma project are split between the various teams and locations. For example Roslin Cells are deriving the GMP embryos needed, and also converting protocols from each team into protocols that will hold up to GMP standards. The Edinburgh and Glasgow teams are working on converting the embryonic stem cells into RBCs and doing this at optimal levels. The NHS Blood and Transplant team are experts in RBC classification and the Dublin team is working towards the scale-up processes. In contrast to many big research projects the Wellcome Trust insisted on a milestone led project plan, which sets out clear goals and deadlines for each of the research stages. Although it is different to their normal way of working the scientists interviewed welcomed this structure as a way of motivating and coordinating the team. Many also felt that the Wellcome Trust had taken a big gamble giving the project the funding it needed, for which they were extremely grateful, and saw the milestones as a way of the Wellcome Trust ensuring that scientific progress was made.

Cultured blood work has been attempted by others (Olsen, Stachura et al., 2006; Lu, Feng et al., 2008). The creation of a stem cell line possessing an O negative blood type has been slow because this genotype is reasonably uncommon in the human population (The National Blood Service puts the proportion of people with an O negative blood type in the UK population at around 7%. National Blood Service (date unknown)), and therefore also uncommon in the embryos used for research. The ultimate result of this work could be the generation of haematopoietic stem cells with the capacity for extensive proliferation, which in theory could repopulate the whole haematopoietic system from the injection of a single cell (Olsen et al., 2006). This is because haematopoietic cells have the ability to form all the different cell types present in the human blood system; therefore, if a single cell had the potential to both replicate and differentiate (the definition of a stem cell) it could repopulate the entire blood system. This work has been referred to as a 'donorless source of cells' (Lu et al., 2008), meaning that it will negate the need for human blood donations. However donations in the form of tissue from embryos are required in the initial creation of the stem cell line. One of the biggest competitors to the BloodPharma research team is the Paris based team headed by Prof. Luc Douay,

which is also developing stem cell derived RBCs and have shown that they can survive in mouse models (Giarratana, Kobari et al., 2005). Other relevant RBC research projects include teams attempting to mask RBC antigens, making any donation universal and able to be given to any recipient (Hortin, Lok et al., 1997; Nacharaju, Boctor et al., 2005).

Cultured RBCs are seen to overcome some of the challenges introduced in the previous section of this chapter:

- Removing reliance on donors – reducing the requirement for altruistic donations and the potential for Transfusion-Transmissible Infections which are a risk with these types of transfusion.
- Reducing the need for blood typing – if cultured blood of the 'universal donor' blood type could be produced then this would minimise the requirement to bloodtype patients.
- Improving storage – it is expected that the cultured blood will keep for longer than current donated blood.
- Benefiting target populations – certain blood disorders are expected to benefit from the cultuRBCs, over and above the general population. These target groups will be discussed in Chapter Four.

The BloodPharma team is seeking to develop blood that is safe, cost effective and publicly acceptable. The scientific research needed to bring this product to market necessitates forward thinking and imagining a development pathway for a product that does not yet exist. Brown and Kraft (2006) talk of 'promissory pasts' of blood stem cells, whereas here we see instead 'promissory futures'. Target markets and potential funding are being considered some years before there is even a product to market. Much of this forward thinking is necessitated both by the programme of research work that must be identified, planned and undertaken, and also by the future impacts of current work. Throughout the early stage lab work the team is looking ahead to the requirements of the regulatory system for future animal and human clinical trials. This brings with it huge challenges for scale-up and uncertainty about the potential target markets, a few of which have been identified. Cultured RBCs are

expected to be identical to in vivo RBCs, and promise in many ways to be better. The BloodPharma team has identified a number of advantages to cultured RBCs, including eradicating the risk of infection and improving patient specificity. The BloodPharma case study allows us to follow a single substance, blood, and the work of a research team as they seek to develop a viable stem cell therapy in the context of over a hundred years of blood regulation and thousands of years of blood use.

Introducing the Substantive Research Chapters

Chapter Two - Methodology and Analytical Framework

This chapter discusses the methodological and theoretical approaches used during this thesis and the collection of empirical data. A mixed method approach was used during empirical data collection, comprising interviews, desk based research, laboratory observation, and participant observation.

Chapter Three - Early Stage Laboratory Work

This chapter looks at the work achieved by the BloodPharma team in the early stages of product development. Blood as a biological entity is introduced, as well as the properties which make cultured RBCs a good target for stem cell research. Interview and observation data are drawn upon to discuss the biological challenges which are identified by the project team. Tacit knowledge is seen to play an important role in the work conducted by the team across multiple laboratory sites. The use of the human body as an examplar is introduced and the distinction between the 'synthetic' blood produced in the laboratory and 'natural' blood is discussed. The important role of expectation and vision is shown in the context of the BloodPharma team imagining a product goal which may be twenty years down the line.

Chapter Four - Imaging and Shaping Final Products and Future Markets

Challenges exist in the scale-up and automation of the cultured blood product, requiring large amounts of forward planning even before the basic product has been developed. The clinical trials for pharmaceuticals and stem cells will be discussed more broadly, showing why the biological properties of stem cells may make traditional clinical trial methods inadequate. This uncertainty is felt by the

BloodPharma team as it must look ahead to plan trials, a suitable paradigm for which does not yet exist. Target populations which have been identified are discussed as a potential first step towards the long-term goal of replacing the blood transfusion service, and because the cultured blood product may benefit these groups above others. The long-term goal is to replace the blood donation required by the current transfusion services, but already the project team are looking beyond this to other potential innovations.

Chapter Five - Regulation in the BloodPharma Project

The UK has a well developed system for the regulation of stem cell research and this chapter addresses historical events which have been instrumental in shaping this current system. Drawing on interviews with regulators and scientists outside the BloodPharma team, both the benefits and constraints of the regulatory system are identified. The chapter then focuses more specifically on the impact of regulations on the BloodPharma team, addressing specifically the knowledge and expertise required to navigate the regulatory system. The cultured blood product will bring with it specific risks which will impact on the way it is perceived by regulators and the future hurdles which the team will have to overcome to bring their product to clinical use. In the face of uncertainty the scientists often seek to anticipate future concerns before they have been articulated by the regulatory system.

Chapter Six - Public Engagement in the BloodPharma Project

Throughout the BloodPharma project the team has engaged in public outreach, which was a stipulation of the Wellcome Trust grant. The role of funding bodies in the motivation for scientists to do public outreach will be discussed more widely, before the specific motivations and expectations of the BloodPharma team are introduced. The outreach events attended and my role as a participant observer are discussed, as well as drawing on the experiences of the scientists stepping outside their normal area of expertise to engage with the lay public. The BloodPharma team has the difficult role of balancing current downstream engagement with current technology, specifically the need to promote the cultured blood project without undermining the current blood transfusion services and their reliance on human donations.

Chapter 7 - Conclusion

The concluding chapter of this thesis draws together the main themes from the substantive chapters and reviews the overarching research questions. The relevance of this work to the innovation/regulation/policy triangle is discussed and suggestions for further work introduced.

CHAPTER 2: METHODOLOGY AND ANALYTICAL FRAMEWORK

In this chapter I provide a description and justification of the methods and analytical framework used for this study, and outline some of the key literature relevant to the themes in each chapter. I also reflect on some of the opportunities and challenges of working closely with a scientific project team, whilst at the same time studying them.

RESEARCH STRATEGY

This thesis comprises an in-depth case study of the development of a cultured RBC product which is being undertaken by the BloodPharma team. In designing my research I drew upon previous work involving case studies and laboratories, particularly Latour and Woolgar (1986), Pfeffer and Kent (2006) and Collins and Kusch (1995). I was particularly interested in becoming immersed in the work of the team through a mixed method approach. Mixed method or multi-strategy research is often assumed to imply a mixture of qualitative and quantitative research. In this project, however, I will use the term to refer to the use of a variety of qualitative methods including desk based research, interviews, lab observation, public outreach, conference data and a dedicated case study.

It must be acknowledged that there is some contention over the use of multiple methodologies, which is summarised by Bryman (2004) as resting on the idea that different methodologies come from different epistemological positions. In choosing to employ a particular method the researcher is not just choosing the practical undertakings of that method but the epistemological assumptions that come with it, and these assumptions may not be the same for different methods. I accept the idea that different methods will bring with them different epistemological assumptions, but this does not mean that mixed methods should necessarily be avoided.

The area of stem cell research is extremely complex, involving many actors and stakeholders, and it would be a serious error to assume that one methodology has any hope of capturing all relevant data. Although interviews and desk based analysis

alone would have enabled a good, general assessment of the work of the BloodPharma team it would have lacked sufficient depth and failed to capture the full range of alternative perspectives. Like most professions, the important discussions in science are as likely to occur informally over lunch at a conference as they are in a formal team meeting, and it was this additional subset of information that this research set out to capture.

Another reason for a multi-method approach was as much for my own benefit as it was for the quality and range of data. Using laboratory observation, for example, allowed me to see the tools used and the stem cell lines developed, which contributed to a greater understanding of techniques mentioned in interviews and journal papers. An important point to mention when discussing this use of multi-methods is that the entire data collection process was highly iterative. All the methodologies were used over the whole data collection period, rather than in discrete blocks. This allowed the experience of one data collection method to inform another and made for more in-depth data collection. For this reason particular methods are not associated with particular research questions, as the project was designed to use an inductive approach allowing the data to inform the conclusions, rather than working to a pre-supposed hypothesis.

THE METHODS USED

Below I explain in turn the different methods employed during the data collection period, although as mentioned above they were used in a highly iterative way and are grouped into discrete subheadings for presentational purposes only. After an explanation of each method I shall discuss issues of reflexivity and ethics which are common to all the data collection methods described.

The Case Study

The Wellcome Trust BloodPharma project forms the case study for this project. This is a basic research project seeking to develop cultured RBCs (RBCs) from human embryonic stem cells, for the purpose of transfusion. It is a multi-lab project led by the SNBTS and involves research teams in Bristol, Edinburgh, Glasgow and Dublin, as described in detail in Chapter One. This particular case study was chosen for a number of reasons. On a practical level the co-sponsorship of the PhD by the SNBTS allowed a level of access to the project team that would not have been possible without this gate keeping role. As an example of a stem cell therapy project it was also unusual, involving many researchers from different backgrounds and geographical areas. It represented a full circle, from the earliest blood transfusion experiments to the development of blood as a cultured product, the dawning of a new era in potential stem cell therapies, and the attending public reactions to this. The timing of the project was also an important consideration as the BloodPharma project was at the beginning of its funding when this PhD started, meaning the case study allowed a stem cell therapy to be followed through the initial biological hurdles, whilst looking forward to the future regulatory challenges. Finally RBCs are short lived in the body and contain no DNA, but yet are required in enormous quantities, posing interesting challenges for future scale-up, clinical trials and regulation.

In accordance with the iterative mixed-method setup of this PhD the case study was considered from a number of methodological angles.

- Interviews with the heads of laboratories elicited in-depth information on the role of each laboratory, the biological hurdles faced and their experiences of the regulatory system.
- Laboratory observation allowed further discussion with other researchers, including technicians and PhD students. They also allowed me to see first hand the workings of the laboratory.
- Public outreach allowed me to witness the BloodPharma team projecting their 'public front' and representing their work to wider audiences.

- Meetings/conferences allowed discussion with the BloodPharma team about new ideas, and revealed the methods and strategies used by researchers to disseminate their work to others within the team.

The use of the case study provided in-depth data about the BloodPharma project. The project itself is ongoing and so the aim of this study has been to provide a 'snapshot' of the project over a three year time period, from the autumn of 2009 until the end of 2012. As the BloodPharma project is still ongoing I may occasionally use the present tense to refer to work being undertaken by the team. This case study set out not to produce an example of experiences which can be extrapolated to all research teams, but instead to embrace the phenomological approach, to 'seek to discover some of the underlying structure or essence of that experience through the intensive study of individual cases' (Thorne, 2000). In other words my aim was to unpick the mystery which often surrounds the development of stem cell therapies by focusing on the individual case of the BloodPharma project. The single case study method is also recommended by Yin (1994, pg.40) where a case study represents an 'extreme or unique case' or a 'revelatory case'. The BloodPharma project is unique amongst other stem cell research projects due to the biological properties of RBCs, the presence of an established donation system, and the large scale-up challenges. For this reason it not only represents a unique case study but also a revelatory case as it challenges the current ideas of appropriate regulation for stem cells.

Interviews

It was decided that semi-structured interviews (Fontana and Frey, 1994) with key participants would be beneficial in eliciting information that it would not be possible to obtain through desk based analysis alone. Interviews took place both with primary members of the BloodPharma team and also with persons involved in the regulatory system, plus other stem cell scientists and relevant stakeholders. In total there were 18 interviews, one of which included two participants. Three interviews took place via the telephone, the rest were conducted face-to-face. On average each interview lasted for around one hour, with a recording time of around 50 minutes. The shortest

recording time was 33 minutes, the longest 86 minutes. A table of interviews and the relevant stakeholders is shown in Figure 1.

The SNBTS co-sponsorship of this project was instrumental in allowing access to the researchers. All those who were involved in the BloodPharma project were willing to be interviewed, the only difficulty being arranging a convenient time. Other potential interviewees were identified at conferences, meetings or through recommendations

Figure 1: Interviews. Showing the interviews undertaken during data collection

No.	Affiliation	Type	Background
1	Alternative stem cell project Interview 1	O	Med
2	Alternative stem cell project Interview 2	O	Med
3	Blood Expert	O	Med
4	Blood Pharma Regulatory	CS/R	Reg
5	BloodPharma PI	CS	Lab
6	BloodPharma PI	CS	Lab
7	BloodPharma PI	CS	Lab
8	BloodPharma PI	CS	Lab
9	BloodPharma PI (Double interview)	CS	Med
10	BloodPharma PI Interview 1	CS	Med
11	BloodPharma PI Interview 2	CS	Med
12	Consultancy	R	Reg
13	Regulatory	R	Reg
14	Regulatory	R	Reg
15	Regulatory	R	Reg
16	Regulatory	R	Reg
17	Regulatory	R	Reg
18	Regulatory	R	Reg

from other participants and colleagues. In this way most interviewees were first approached in person to see if they would be willing to consider taking part in an interview. This initial meeting was then followed by an email explaining more about the project, explained their rights to confidentiality and included a copy of the consent form for them to study at their leisure. Two digital voice recorders were used for most of the interviews, apart from the three telephone interviews which relied on

hardware to connect the digital recorders to the phone line. Recording interviews allowed the interviewer to listen to the participants without the added difficulty of trying to take notes, and made for a more responsive interviewing technique. One respondent did not wish to be recorded and so notes were taken during the interview, which were subsequently emailed to the interviewee for clarification. Another interview was not recorded due to some unknown background interference which caused both Dictaphones not to work, so notes were taken instead. Recorders were turned on with the interviewee's permission and after the consent form had been signed. They were turned off at the last possible minute, as interviewees had a habit of mentioning something important the moment that recording had stopped. Any points mentioned at the end of the meeting were noted down and added to the bottom of the transcribed interview.

The interviews for this project were all with 'elite' participants, but what constitutes an elite is often hard to pin down from the literature. For the purposes of this project all the interviewees were considered to be 'elites' – men and women who were chosen because they are experts in their field. Interviews with elites do not pose the same methodological challenges that are experienced when interviewing lay or vulnerable people. They are distinct from the 'caring interview dialogue' discussed by Kvale (2006) for example, that gives a voice to the marginalised and empowers participants. But interviews with elites pose unique challenges that can be just as difficult to overcome and deserve consideration here. The interviews did not pose great challenges in terms of consent, ethics or safety. The interviewees were highly educated and capable of understanding and questioning the consent forms given, they were also in positions of responsibility that left them unlikely to be coerced into taking part against their will. The interviews generally took place in work situations, with the interviewees well known to the scientific and research community. One interview took place at the researcher's home and in that instance a safety telephone call was arranged between the researcher and somebody back in the department.

Smith (2006) talks of her surprise when realising how easily two groups of researchers could categorise their participants into those who 'possessed power' and

those who were ‘disempowered’. To somebody who has almost exclusively interviewed elites this does not seem so surprising, and those who were interviewed for this project definitely fell into the ‘possessing power’ category. The main methodological challenge to interviews with elites is identified by Desmond (2004) as stemming from ‘the power differentials between the researcher and the researched’. She identifies the power relationship between researcher and researched as ‘inevitably asymmetrical’. This was certainly evident when interviewing those who took part in this project – they projected the image of the confident interviewee entirely secure in their knowledge of the subject and not in the least bit intimidated by being faced with an interviewer and a tape recorder. Smith (2006) mentions that another problem of ‘interviewing up’ is the ability of elite interview participants to protect themselves and to manipulate data. Throughout the interviews I was alert to this, especially as at the time interviews were commencing the BloodPharma team had received a large amount of unplanned media attention when the details of the project had been accidentally leaked. This resulted in a press release being put together at short notice and the team therefore had a good coherent ‘story’ to use.

Although on the lookout for this skewing of data I did not feel that it ever happened, all the interviewees appeared to be extremely open with me about their views, even if that meant going against the established or publicly articulated view. The power imbalance between myself and the interviewees also led me to place greater emphasis on my own scientific background as a way of demonstrating my credibility. However, there were instances when the greater power held by the interviewee could be put to good use, often ‘playing ignorant’ elicited more of a response as they attempted to explain their work to me as a lay person. Elite interviews are generally conducted with people who are extremely busy and coordinating timings of interviews can be problematic, in addition most elites are non-replaceable. With elites it is possible that only one person in the country may be able to answer your questions, which leaves little room for manoeuvre. Meeting people face-to-face before following up with emails did help the response rate, and nobody that was approached turned down the request for an interview, although setting a convenient time did prove difficult in some cases.

Interview data were transcribed by myself using Express Scribe transcription software. Respondent's replies were transcribed verbatim, but with the removal of hesitations, filler words, and non-verbal sounds (Roberts Powers, 2005, pg.67) unless they gave added meaning to the sentence. Grammatical inconsistencies were kept. Questions and general 'chat' that were not relevant to the interview were shortened or tidied. Transcripts were analysed using the inductive approach described by Bryman (2004, pg. 8-10), allowing the data to drive the conclusions rather than a reliance on pre-prepared hypotheses. Initial reading and re-reading of the interview transcripts allowed the main themes of the interviews to be identified (Strauss, 1987, pg.35). Transcripts were then loaded into NVivo and coded more systematically using thirteen nodes:

- **Clinical trials** – information on clinical trials related to the BloodPharma product or stem cell research more generally.
- **Clinical trials (ReNeuron)** – information specifically related to the clinical trial phase of the ReNeuron project.
- **Changes after use** – proposed changes to the BloodPharma product after initial use.
- **Imagined regulation** – potential regulatory concerns for the BloodPharma product and other stem cell research.
- **Interdisciplinary** – incidences of interviewees referring to the interdisciplinary nature of the BloodPharma project or working together with other members of the team.
- **Product** – information regarding the BloodPharma product, including references to who will produce and pay for the eventual product.
- **Scale-up and production** – information from interviewees regarding the scale-up and production challenges for the BloodPharma product.
- **Tacit knowledge** – incidences where interviewees mentioned the use of tacit knowledge.
- **Public** – mention of ethics, public understanding, requirement to carry out public engagement etc.

- **Naturalness** – where interviewees referred to the natural/unnatural/synethitic distinction of the BloodPharma product and other stem cell therapies.
- **Regulation (Case Study)** – information about interactions between the BloodPharma product and the regulators.
- **Regulation (Other)** – information from other interviewees about interactions with the regulatory system.
- **Regulation (Regulators)** – views from interviewees involved in the regulatory system regarding the regulation of stem cell products.

Transcripts were also categorised depending on the background of the interviewee (as shown in Figure 1.), which allowed for easier cross-referencing. These groupings were:

Case Study (CS) – individuals directly involved in the BloodPharma project

Regulatory (R) – individuals involved in the regulatory system

Other (O) – interviewees with other backgrounds, for example blood specialists not related to the BloodPharma project, clinicians and consultants

Within these three groupings the interviewees were also divided further into laboratory (Lab), regulatory (Reg), or medical (Med), to reflect the occupation of the individual. Throughout the thesis these groupings are used to reflect the background of the individual from whom quotations are taken, for example (CS/Med) indicates and individual involved in the BloodPharma case study but who has a medical background.

Laboratory observation

The importance of visiting laboratories is becoming widely acknowledged as contributing to robust data collection methods for projects involving the study of any scientific innovation. The decision to use lab observation for this project stemmed initially from Pfeffer and Law's (2006) paper on blood tests. This paper raised a number of issues which were important in the study of biological innovations, as well as having the added bonus of also being about the study of blood. The writers had made the decision to follow the blood tests through the laboratory process to get

an understanding of what happens in the translation of physical blood to computerised data. I felt this opened up new ways of understanding the scientific process, by focusing on the product as much as the researchers. Visiting the laboratories involved in the BloodPharma project was an important part of the data collection. The labs in Bristol, Glasgow and Edinburgh were chosen because of their role in the basic research component of the project. The visit to Bristol had to be combined with a morning of interviews, whilst the Glasgow and Edinburgh visits comprised a whole day each.

Not only did these visits provide me with a fuller understanding of the laboratory environment but it also helped with the analysis of interview data. When an interviewee is miming cutting up a batch of cells (for example) they often assume that you can visualise that mime too, that you are familiar with the tools they would be holding and the environment that they would be in. This is only possible if you have at some point been there with them. It is also only through seeing the researchers in action that a fuller picture emerges of just how much of this technology relies on tacit knowledge and human observation, and how this is such a huge hurdle to overcome when discussing the automation of these techniques. Access was not problematic due to the good working relationship with the BloodPharma team, however the impression given was that the basic researchers were unsure about what I would be looking for and how they could help. It was difficult for them to understand that what was completely obvious to them (because they worked in that situation every day) might be interesting to outsiders.

Observation in the laboratory was considered a casual data collection activity (Yin, 1994, pg.86), and data collected was treated as supplementary evidence to interview data. Notes were taken as often as possible during visits to laboratories or during meetings. Care was taken to minimise disturbance to staff, especially when they were carrying out laboratory based work. Notes were kept of initial impressions of the laboratory space and my own reflexive feelings regarding the laboratory visit. A folder of loose paper was collected, which comprised notes taken during visits or meetings, information and drawings given to me by the project team, leaflets and

conference information etc. This was considered a supplementary data source and was referred to using an iterative process (Thorne, 2000),in order to develop a comprehensive understanding of laboratory practices, how researchers organised themselves within the laboratory space, and presented their work to others. As in Okely (1994, pg.21) the material collected during this observation was used as a 'trigger' to remember experiences which are impossible to commit to paper. The use of drawings and images by the BloodPharma team in early stage laboratory work is discussed in more detail in Chapter Three. These images were collected during time spent with the team during meetings and one-to-one interviews.

Documentary Analysis

This project necessitated a large amount of desk based analysis above and beyond the normal academic journals. For example the official reports of the governmental bodies were extremely helpful, especially the Human Tissue Act and Human Fertilisation and Embryology Act reports. The official websites of the regulatory bodies also contain information on their remits and links to many of their official documentation, such as financial reviews and occasionally publicly available inspection reports. Both the scientific and the social science literature were drawn upon during this work. Such documents provided additional insight as they are considered artefacts, they were written in order to 'do something' (Hodder, 1994), and in this case often represented the 'public face' of an organisation.

Conference and Meeting Data

Attending a wide variety of conferences, talks and workshops on relevant subjects has been an important part of this project. Although the presentations themselves are clearly important in keeping up to-date with the current research field it has often been networking that provides much of the interesting data. Most researchers appear to be more open in their frustrations when in a more informal setting. Very often the same researchers would talk at different conferences throughout the year, and it was interesting to see how their work progressed throughout the course of this project. Smaller meetings were also attended, such as those organised by the Scottish Stem Cell Network, which were often focused on a smaller area of research. I also sat in

on one day of the Penrose Enquiry public hearings, which took place in Edinburgh. This enquiry is looking at the events which led to a number of patients being infected with Hepatitis C and HIV from blood and blood products. Notes were taken during conferences and meetings and a record made of any interesting points or observations made by those in the research or regulatory community.

Public Outreach

The BloodPharma project has been committed to public outreach since its inception and was chosen to exhibit at the prestigious Royal Society 350th Anniversary in London in 2010. The team also took their exhibit to the Big Bang Science festival and the Glasgow and Edinburgh 2011 Science Festivals. More information on the public outreach ventures is discussed in Chapter Six. Throughout these outreach activities I took the role of a participant observer, both studying the team and being directly involved as a member of the outreach team (Atkinson and Hammersley, 1994). Joining the team for these outreach activities benefited the PhD data collection in a number of ways. Firstly it allowed me to talk with members of the general public regarding the BloodPharma project and their reactions to the proposed technology. Secondly, it helped to establish a better relationship between myself and the rest of the BloodPharma team, not only in working together as a team during the exhibitions but also because there was the necessity for meals and socialising together. Thirdly, it provided the opportunity to hear the researchers themselves talk about their work to others. This included members of the general public and those with more scientific backgrounds who came from other stands at the exhibition. At many of the public outreach events I was given the task of taking photographs and asking visitors to the stand to fill out photography consent forms and feedback forms. I would also talk about the project to members of the public if there were no members of the scientific team available. This worked well because it allowed me to chat to visitors after they had seen some of the information available and to ask them more questions about their attitudes towards the project.

REFLEXIVITY

Guilemin and Gillam (2004) quote Bourdieu in explaining the process of reflexivity as taking two steps back from the research subject, to question not just what one knows but how one knows it, and what shapes our knowing. Throughout this project I have tried to be reflexive about my own background and the way that it influences my outlook. My first degree was in Genetics, before I subsequently moved to Science and Technology Studies and this has undoubtedly had a bearing on the way that I 'know'. From a world where bias in research was focused on tangible influences like temperature or apparatus or researcher technique it came as a struggle to analyse my own background as influencing my work. Indeed the fact that I struggled with the idea of reflexivity forced me to be more reflexive throughout this project. I tried to get into the habit of recording my feelings about each interview as soon as possible and to recognise how my own views might colour my perceptions of data. For some years now I have straddled the boundaries between science and social science, but I still baulk at being referred to as a 'social scientist'. I was conscious that I always mentioned my background in science first, as if to give myself credibility in the eyes of those that I was talking to. Indeed I think that people were more open with me when they knew that I understood some, if not all, of their jargon – that I was 'one of them'.

Participant observant took place through assisting the BloodPharma team with their public outreach, as shall be discussed further in Chapter Six. Throughout the participant observation work I attempted to be reflexive about my own position as one of the outreach team, acknowledging that I found it difficult to be objective at the same time as fulfilling my role as a 'promoter' of the cultured blood project. I did not however find this attachment to the BloodPharma project to be a hindrance. Indeed my interest in the ethical and social implications of stem cell research allowed me to question the BloodPharma project in some respects, whilst still remaining excited about the overall innovative potential. I am in agreement with Yin's (1994, pg.88) observation that using participant observation gave me the chance to see the 'viewpoint of someone 'inside' the case study'. I also took comfort from Becker's

(1967) paper that acknowledges that it is impossible to work in a neutral and value-free way, instead I sought to use my attachment to the BloodPharma project to do the best outreach that I could achieve, whilst also being aware of this attachment and the forms that it took. Establishing a close relationship with the BloodPharma team has in many ways set this project apart as unique. In having the opportunity not only to interview and watch them, but also to socialise with them, to plan outreach activities, and to meet at conferences has contributed hugely to the project. As they now know me they sometimes send me information I might be interested in or pass on interesting knowledge when we meet.

ETHICS, DATA PROTECTION, CONFIDENTIALITY

Guillemin and Gillam (2004) place great emphasis on 'ethically important moments' in research and believe that projects involving human participants start from a position of 'ethical tension'. This did not appear to be the case during this project, which potentially comes back to the issue of interviewing elites and the way in which these interviews differ from those with more vulnerable participants. At some points I found myself attempting to overcome ethical tensions that were not really there – for example in the decision to anonymise the data as much as possible despite participants being happy to be named. I was concerned that they may not understand the implications of things they had said, or were so relaxed that they did not realise people could potentially use that data against them. One interviewee took a telephone call during an interview and proceeded to have what sounded like an extremely confidential discussion, in the full knowledge that I was in the room and the tape recorder was running. All interview recordings and transcripts were kept in a locked cupboard at the Innogen Centre or were stored on a password protected computer. Files were saved onto the University server which protected them in the event of a computer failure. The main issue of concern during this project was protecting the confidentiality of respondents. Many of them had few issues about being identified and were happy to be named, however the decision was taken to annonymise all the participants as fully as possible. Care was also taken during interviews not to

mention other participants by name but just to refer to them as members of the research or regulatory communities.

THEORETICAL AND CONCEPTUAL FRAMEWORKS

Alongside the methods that were used to gather empirical data for this project it is also necessary to consider the theoretical frameworks which underpin the analysis of this case study. Just as this project has used a mixed methods approach to gather data in different ways so I have also identified different theoretical concepts which have been used throughout the research. Drawing on concepts of grounded theory (Strauss and Corbin, 1994) the data collected was used to drive the theoretical framework used for each chapter, taking care to avoid what Gilbert (2006) terms 'theoretical arrogance' in attempting to force theory to fit observations or vice versa.

Science and Technology Studies (STS) seeks to 'explore technology in a wide range of fields' and to analyse relationships between the actors involved in creating and using such technologies (Brown and Webster, 2004, p.29-30). It is sometimes referred to as opening the 'black box' of technology, to look deeper at technologies themselves rather than their impact on the social world. The case study element of this project draws on this idea of the black box, as through in-depth investigation of the actors and technology involved in the BloodPharma project a clearer understanding of the development and translation of a stem cell therapy can be developed. I shall identify the theoretical concepts that have been of most relevance to the themes within each of the substantive chapters.

In Chapter Three the theories of tacit knowledge and expectation contribute to an understanding of early stage laboratory work. The BloodPharma project is introduced as an example of interdisciplinary working across multiple research spaces, drawing on Lyall et al. (2011) in order to demonstrate that this project fits the label of 'interdisciplinary' working. The volatile nature of stem cells and the mixed grouping of the team mean that tacit knowledge is an important consideration in the development of early stage laboratory processes. Many of the findings reported by

Collins are evident in the day-to-day work of the BloodPharma team, showing that his conclusions are relevant across different decades and scientific disciplines. For example the BloodPharma team is an example of Collins' (1974) observation that scientific communities share within themselves large amounts of tacit knowledge, and indeed in this case study it can be seen that this tacit knowledge is shared at an even deeper level, within laboratories and even by individual scientists. The exchange of staff members between laboratories is an example of the importance of 'personal contact' identified by Collins (2001) in his work on the quality factor of sapphire. The importance of tacit knowledge within this early stage laboratory space leads to a recognition of the ultimate goal of standardisation within the stem cell field, and the problematic nature of this goal, as identified by Webster and Eriksson (2008) and Eriksson and Webster (2008). For the BloodPharma team the use of images is identified as a main route towards higher standardisation between laboratory members, in similarity to Lösch's (2006) case study of visionary images as communication in the nanotechnology sector.

The *in vivo* RBC is identified by the BloodPharma team as an exemplar, or benchmark, for which their early scientific work is aiming. Here I view this through the idea of 'bioequivalence', as it is discussed for the technology surrounding Genetically Modified crops by writers such as Meredith (2003) and Millstone et al. (1999). Bioequivalence leads us to question the 'naturalness' of the cultured blood product, in comparison to both donated RBCs and chemical blood substitutes. Although the public response to the BloodPharma product is not yet certain I draw on the work by Douglas (1966) to explore some of the concepts around 'dirt' and 'matter out of place' in anticipating potential reactions to the cultured blood product. In the final section of Chapter Three the importance of expectation in early stage laboratory work is introduced. Foresight is seen as crucial in mobilising funding (Anderson, 1994), and building the shared bonds and expectations necessary for project coordination (Bidault and Cummings, 1994; Borup, Brown et al., 2006).

Chapter Four explores further the standardisation of stem cell research to consider the challenges of automation identified by Webster (2008) and Placzek et al. (2009).

The contrast is seen here between the standardisation required for automation and the 'whatever works' approach (Shaw, 2010) to early stage laboratory research identified in Chapter Three. Such standardisation requires an acknowledgement of the importance of path dependency and 'lock-in' (Liebowitz and Margolis, 1995). Work by Webster and Eriksson (2008) and Eriksson and Webster (2008) shows the difficulty of standardising stem cell research, but the outcome of an attempt to standardise stem cell research is the problem of 'lock-in' to a particular protocol, resulting in a loss of biological diversity in the stem cells themselves and tacit knowledge for the researchers.

Whilst the BloodPharma team continue to work towards a workable scale-up solution for the cultured blood product, uncertainty still surrounds the clinical trials route, which represents one of the main hurdles in the translation from laboratory to clinically useable product. Uncertainty particularly surrounds the appropriateness of animal models for the BloodPharma product, and for the stem cell field as a whole, questioning the idea of 'nature implied' (Lynch, 1988; Hansen, 2006; Davies, 2010) and the laboratory as a 'sub-place' (Asdal, 2008). The BloodPharma process represents a change to the established method of obtaining blood from human donation, yet as a product is can be considered a continuation of an established use, albeit obtained from a different source. The survivability of the stem cell field more widely depends on the cost effectiveness of therapies and on the future regulatory system for such products (Tait, 2007). One method of introduction is likely to be the identification of key target markets. The team are also imaging futures beyond these initial markets, visualising a series of goals such as the use of adult cells as the starting source material. As in Chapter Three the use of informal anticipatory procedures is considered necessary in the bringing together of the team and identifying future translation goals. In addition we see here the teamwork between scientists and clinicians, identified by Wainwright et al. (2006) as key to the translation process from bench to bedside.

Chapter Five focuses on the interactions between the BloodPharma project and the wider regulatory system for stem cells. Croley's (1998) theories of regulation are

used as a basis for understanding the creation of different types of regulation, with consideration of the formalising of 'good practice' using Messner (2009). Chataway et al. (2006) is used to explain further the precautionary and reactionary methods of regulation, with further discussion of the precautionary method of regulation drawn from writers including Majone (2002) and Levidow (1996). The regulation of stem cell products is seen as an exercise in boundary work (Williams, Wainwright et al., 2008), with stem cells considered to be traversing boundaries (Cooper, 2004) and requiring the reordering of regulatory boundaries (Brown and Michael, 2004). Expertise is also a crucial part of the regulatory relationship, with expertise required by the regulators and especially by the scientists in navigating the regulatory system. There is also a distinction seen between the formal expertise achieved qualifications and the hands-on expertise of those who work on a day-to-day basis with the cells, in a similar fashion to Wynne's (1992) sheep farmers and the subsequent discussion of expertise by Collins and Evans (2002). In the latter part of Chapter Five I discuss the BloodPharma product in the context of specific risks, using as a basis Sadler and Zeidler's (2005) model of 'informal reasoning', to explain how the BloodPharma team discuss the specific risks related with their work.

In Chapter Six the public outreach work carried out by the BloodPharma team is discussed, beginning with an outline of the objectives behind public outreach. Engaging with the public is viewed as a way to minimise future risk perceptions of the product, as alternative blood products were found by previous studies (Fleming, Ferguson et al., 2007; Ferguson et al., 2008) to be perceived as riskier than conventional transfusion, and prevent a resurgence of the direct action groups which became synonymous with the proposed introduction of Genetically Modified crops (Grant, 2004). Public outreach is considered to be moving away from the 'public deficit model' (Sturgis and Allum, 2004) towards an increasing focus on engaging the public in scientific decision making (Irwin, 2001). This causes us to question the role of the scientist as public communicator and the support given by institutions for researchers to carry out this role (Mathews, Kalfoglou et al., 2005). The outreach work carried out here demonstrates the challenge of upstream engagement (Tait, 2009), especially considering the presence of the already established technology of

human blood donation. The team therefore have to balance the dual message of promoting both a novel technology, whilst seeking to keep public faith in the current donation system.

This thesis is interested in exploring the different interests and choices of those involved in the stem cell field, and as such draws on (although is not driven by) a SCOT paradigm. Social Construction of Technology (SCOT), acknowledges that what we accept as scientific 'fact' has been created through this process of social shaping and that writers make knowledge claims that are accepted or rejected by the academic community around them through negotiation (Myers, 1985). This is in addition to recognising that all technologies are socially shaped through the 'choices' that are made during the design of technology and between different technologies (e.g. in the market). This is known as Social Shaping of Technology (SST) and is explained in more detail in Williams and Edge (1996). SCOT is an important concept to acknowledge in a study that examines an area of research that is going through a period of both scientific and regulatory shaping. Many of the decisions required throughout the regulatory process build on the perspectives of the actors involved, and decisions that are taken over how to regulate, over what are considered acceptable standards of safety, about what previous technologies could be used as comparisons etc. Boundary Work (Gieryn, 1983) is acknowledged in Chapter Five on regulation, but in thinking reflexively about how I carry out my data collection I have to acknowledge that I often started from an assumption that boundaries between organisations, and the way that they maintained these boundaries, are important. This is reflected in the way that I instinctively grouped my proposed interviews for this project in to 'researchers' and 'regulators', even though the boundaries between these groups may be more blurred than they initially appear.

This chapter has introduced the methods that were used for gathering the empirical data and some of the most appropriate theoretical perspectives for analysing these data. The following Chapter marks the beginning of the four substantive empirical chapters.

CHAPTER 3: EARLY STAGE LABORATORY WORK

INTRODUCTION

The BloodPharma project team is seeking to develop a final product that is standardised, controlled, clean, and meets required regulatory standards. However, the reality of early scientific development is instead a story of scientists working together and 'muddling through' to overcome enormous scientific and technological challenges. Muddling through refers to the making of small incremental steps rather than having a defined plan, for example Lindblom (1959), Bendor (1995), and Fortun and Bernstein (1998). Walking into a working laboratory is very different from the image of a controlled environment; although scrupulously clean you are likely to encounter desks covered with equipment, teetering stacks of deliveries and every spare inch of space crammed with supplies of gloves and sterile plastic-ware. Walls are covered with notes and schedules, plans for cells feeding, technical pictures, cartoons and posters. It is very clear that the laboratory is a place where people work every day. And the scientists themselves are not standardised and controlled, they have hopes and fears for the project, moments of elation when things go well and panic when they do not. They differ in what they envisage the project outcomes to be, and they argue, gossip and contradict each other. This chapter will use empirical data from meetings, interviews and laboratory observation to tell the story of early stage laboratory development through the words of the scientists.

The overarching research question that this chapter will address is:

How is early stage laboratory work achieved through interdisciplinary, multi-lab working, where standardisation of methods is difficult and where there exists an accepted technology?

Focusing predominantly on the work of the scientists, the chapter will explore how the team constructs and seeks to find workable solutions to the early stage biological challenges, in the context of looking ahead to various imagined futures and product development pathways for the cultured blood product. The BloodPharma project could be described as a paradigm shifting project, as it has a number of key features

that distinguish it from many other types of laboratory research projects. Firstly, it brings together a number of teams physically separated by geography; each contributing different types of expertise to the project. This is a project that highlights the importance, as well as the associated problems, of interdisciplinary working. Secondly, the project is not simply a basic science research project with short-term milestones and deliverables. Instead it has very long-term aims and objectives. The project team are in some cases looking 20 years into the future of the product, so the temporal dimension is crucial and brings both opportunities and challenges. Thirdly, the emotive nature of blood donation and transfusion makes this a socially and politically salient project in which interaction and engagement with the public is given a high priority. Fourthly, the regulatory pathway for cultured blood is still unclear, as blood has certain characteristics (e.g. the lack of nuclear DNA) which set it apart from conventional stem cell treatments. Finally, this project is strongly grounded in the perceived idea of a final product that will be potentially marketed to a large proportion of the population. The expectation is that the development of cultured blood will require industrial level scale-up; thus creating a promissory vision of both jobs and value creation for the UK economy.

The specific areas of regulation and public engagement will be addressed in more detail in Chapters Five and Six respectively, but here I will examine four key themes that are important in the development process of early stage scientific work for cultured blood – interdisciplinarity in practice, the role of tacit knowledge, the construction of a natural/synthetic distinction, and imagined future products. To do so I will draw on data collected from three years of observation of the BloodPharma project and the scientific team, and semi-structured interviews with eight of the principal team members. Each of these four areas shall now be introduced in more detail.

The first section of this chapter will focus on the use of interdisciplinary working amongst the BloodPharma project team. The BloodPharma project is set apart from many standard research projects by its strong focus on interdisciplinarity, with a scientific team spread over many sites and researchers with different disciplinary

backgrounds. This section will identify some of the challenges and benefits that arise as part of working in such an interdisciplinary group.

The second section will draw upon the interview and observational data to explore the importance of tacit knowledge in early stage laboratory research, contrasting these with examples of tacit knowledge from the literature, such as Collins (1974) and Busch (2008), and exploring how the 'tacitness' of stem cells affects the long term development of stem cell products.

In section three I will explore the natural/synthetic distinction that has been operationalised in different ways by the scientists in this project. The BloodPharma project is seeking to make cultured RBCs in the laboratory which are indistinguishable from donated blood, raising questions of whether this cultured blood is natural, unnatural, or synthetic. The role of the human body as an exemplar will also be discussed, along with reflections on whether the natural/synthetic distinctions matter in practice.

In the final section, I will focus on the different ways and contexts in which the scientists imagine the future product development pathways and regulatory requirements. The long-term nature of this project requires that the research team continually look ahead and identify future challenges/roadblocks and ways to mitigate them. In so doing they construct different product imaginaries, a predicted end goal towards which their research is directed. The broader discussion around foresight that will conclude this chapter will lead us into Chapter Three, where the (as yet) imagined world of animal testing and target populations will be discussed.

THE CHALLENGES OF WORKING ACROSS MULTIPLE SITES AND DIFFERENT DISCIPLINARY AREAS

The BloodPharma team operate in four scientific laboratories and multiple office sites, whilst the researchers themselves come from different backgrounds in blood cell research, stem cell research and clinical research/medicine. Covering the entire team is the Wellcome Trust's imposed project milestones, which for many represent

a different way of working and reporting. This section will introduce some of the backgrounds of different team members and identify some of the challenges that arise as part of working in such an interdisciplinary group. It will show that there are contrasting views found in the literature over what constitutes 'interdisciplinarity' and I will introduce some of my own reflexive thinking about my role as an interdisciplinary observer. The empirical data gathered reveals incidences where different researchers base judgements, quite naturally, on their background and experience.

The BloodPharma team initially came together in response to a call from DARPA (the research arm of the American military), which wanted to study the generation of blood transfusions in a battlefield setting. Although the UK team was unsuccessful in obtaining the DARPA funding the project continued under the auspices and funding of the Wellcome Trust. There has been some discussion about the use of the title 'BloodPharma', as this was originally the title given to the project by the DARPA funding call. However the team have continued to refer to themselves as the BloodPharma project whilst under the funding of the Wellcome Trust, so I have taken the decision to continue using the BloodPharma title throughout this thesis. The research project pulled together teams from all over the UK, with differing backgrounds, in the pursuit of this shared goal of culturing RBCs. The Wellcome Trust also imposed milestone-led guidance on the researchers which differed to the way in which many members of the team were used to working. The overall BloodPharma team is comprised of people who specialise in (among other things) blood cell characterisation, stem cell growth and characterisation, GMP compliance, and regulation. The staff is also a mix of clinicians and laboratory scientists, and have backgrounds in both university and industry settings. It is evident that this project has been instrumental in pulling together collaborators who visualise the project, and its outcomes, in very different ways. Case studies such as these allow us to open the 'black box' (Baumard, 1996) of scientific research and to see the boundaries that exist within a single laboratory or project team.

The mixed grouping of the BloodPharma team therefore creates a research environment that is very different to many basic research projects, where researchers often share both a common discipline and single working space. Instead we must look at how research is produced across a mixed team, and such knowledge creation has been divided by Lyall et al. (2011) into three categories:

- *Multidisciplinary:* Researchers from different disciplines contribute to a larger project, but work on separate sections with little collaboration between the partners.
- *Interdisciplinary:* Researchers from different disciplines in a much more collaborative way, learning from each other and creating knowledge which is 'more than the sum of its parts'.
- *Transdisciplinary:* Attempts to move beyond the idea of disciplines to work towards finding solutions to problems without relying on particular disciplinary backgrounds.

Using evidence gathered from the case study I shall consider which of these approaches best characterises the knowledge creation during the BloodPharma project.

Interviews with the Principal Investigators on the BloodPharma project highlight the advantages that the team have gained from working with others outside their discipline.

> *"I mean the challenge of the project, nobody could do it on their own, first of all. So we couldn't get GMP grade ES cells and we can't do the differentiation of erythrocytes and all the erythrocyte characterisation. So, you know, everybody needs each other and I think maybe that's why it has to be a bigger thing, because it does, it covers a huge area, from the GMP grade right to a functional erythrocyte, nobody could have the expertise in all these areas."* (CS/Lab)

The interviewee acknowledges the expertise which must be combined to produce the end product, something which it would be impossible for one team to do alone. Bringing together a larger team from different disciplines allows access to all the years of knowledge and experience that each member possesses.

> *"So in a way we need each other, like the basic scientists need the clinicians to know the regulations, to know the sort of functional clinical*

> *properties of RBCs, but they need us, as basic scientists, because we've worked in the area, in the differentiation area and understand the differentiation and understand the complexities of what you need to do.*"(CS/Lab)

Here the interviewee categorises the team into two distinct groups, the basic scientists and the clinicians. Whilst the basic scientists are seen as having expertise in the physical growing of the cells the clinicians are considered to have the knowledge of application, in how these cells will function, and the regulatory hurdles. Tacit knowledge is discussed in more detail in the second section of this chapter but is alluded to here with the suggestion that expertise is vital for understanding and controlling the differentiation of these cells.

> *"To go from an ES cell to a RBCs…it's a huge, you know, developmental biology project, to do that. So, I guess they need us as much as we…you know it's not a need it's a collaboration, and I think this project's particularly good because I think there is a feeling of equal footing on it, and we all have our expertise, it's appreciated by others and respected, if you like, you know, I think there's a lot of mutual respect between the different PIs because we have got such different expertise, which I think that's maybe one of the strengths of the projects to be honest."* (CS/Lab)

The interviewee is very insistent that this project has a collaborative feel, with everybody on an equal footing. There is not an awareness that this project belongs primarily to one group, with the others being brought in more on a consultant level, and this did appear to be the reality thoughout the project. It is seen that all the areas of expertise are equally valid and appreciated and this combining of expertise is seen as a major contributor to the strength of the project. The respondent here articulates the idea that the BloodPharma project is in some way special, unique and distinct from other research projects in that the research is very broad, aiming towards the derivation of a potential stem cell product, rather than focusing on a narrow part of the scientific work. This wide range of research makes the project very challenging, and relies on input from a variety of expertise, hence the reference to the BloodPharma project being a 'bigger thing' than other research projects. This suggestion that the wide scope of the project is only possible by bringing together people from different backgrounds highlights the importance of both expertise and experience. The respondent makes the distinction between a 'need' and a 'collaboration', with his view being that collaboration is more about mutual respect.

Again the BloodPharma project is held up as being different from other research collaborations due to the mutual respect that the researchers give to each other.

There is a strong focus not just on the research but on the translation, getting all the parts of the project to coordinate to produce the final end product. Differences between individuals from diverse disciplinary backgrounds were highlighted by their approach towards this translation of basic laboratory protocols into methods suitable for industrial production. There appears here to be a distinction between the researchers who are considered to be 'commercial' and those who are purely 'academic'.

> *"It's a strange one, because the grouping is also very mixed. So of course X are, they are academically derived but are really commercial, and there's ourselves, and I've kind of hit the middle ground between commercial and academic with the X program and other funding that we have. And then pure academics. So it's quite a strange grouping."* (CS/Lab)

Academic research more generally is recognised as having poor translation from basic knowledge production to innovation and economic returns, called the European Paradox (Audretsch and Lehmann, 2005). The same is true of the US, where the monumental financial input of the National Institutes of Health into basic research had, as of 2009, resulted in only 84 examples of new drugs or biologics being discovered in the previous 60 years (Gottlieb, 2009). There is a perception of academics in 'ivory towers', engaging with basic research but not with the translation of this research or the wider communities around them (Bond and Paterson, 2005). This would seem to imply that the academic, or basic research, way of working translates poorly into the commercial sector. Academia, however, is also seen as less target driven, contributing more fully to the wider scientific community through papers and teaching, and giving greater autonomy to researchers (Klee, 2001).

A 2012 report highlights that the types of team working common in industry are less well utilised in academia, and that these sorts of team science prioritise the solving of complex problems and the translation of research (The Academy of Medical Sciences, 2012). Certainly the empirical data gathered from the case study shows that

the academic/commercial distinction is emphasised by the different ways in which the two groups work. Those from a commercial background were used to constant reporting, whilst the academics had been more used to self-directing their research. The reactions to the Wellcome Trust milestone-based style of project funding are an example of this:

> *"So we have quite tight milestones and deadlines to meet within the project, which is a kind of unusual way of working, normally in a grant you get the money to do the work and at the end they say 'what did you do?'. Whereas this is like, they keep tabs on what we're doing and 'oh have you reached that mile..' you have to say what your milestones and your goals are over the three years and then, you know, we'll be checked up on to see whether we've met the milestones."* (CS/Lab)

> *"I've got used to the milestone led system, more recently, so I don't mind that at all, in fact I actually find it quite reassuring that we have those checks and balances in place because it's very easy to get three years down the line and not have done what you were supposed to do. So I like that we have that governance system."* (CS/Lab)

Both of these quotes were taken from individuals with a purely academic research background, who had little experience of working with a milestone-led project. In contrast milestone led working was considered normal practice for those that came from a more commercial background. Although not experienced with this sort of project leadership the academics came to value the role of the milestones and appreciated the governance process imposed upon them. In some cases, they considered that the milestones could actually have gone further, for example incorporating regulatory, rather than purely research milestones, or forcing the team to address at each meeting how its work contributed to each of the key goals.

Another distinction manifested in the team, which also appeared to fall within the academic/commercial boundary, was working to Good Manufacturing Practice (GMP). GMP is essential in translating a process from laboratory working to an acceptable manufacturing protocol and it includes such things as formalising the protocol steps and sourcing suitable reagents. Strict requirements for safety testing of stem cell products require cells to be produced to the same consistent standards, relying on control of the process as much as the product itself (Rayment and Williams, 2010). Rayment et al. (2010) also suggest that the cell specifications and

culture conditions are set at the beginning of the process to ensure a consistent product. This paper, however, is concerned with the clinical translation of stem cell products and fails to address the inconsistencies of earlier basic research.

Stem cells are heterogenic by nature and have the ability to differentiate into over two hundred cells types, controlling this process is more art than science (Shaw, 2010). Laboratory bench processes are time-consuming and difficult to scale (Williams and Sebastine, 2005) and culture conditions are continuously varied in an effort to optimise the process. Shaw (2010) refers to this as a 'whatever works' process. Whilst this is perhaps true I feel it does injustice to the scientists who carefully plan and record all their experiments, and therefore I prefer to refer to it as a 'trial and error' approach. The message though is still the same, that there is a difference between the methods employed by those working in basic research and those involved with the translation of that research to produce a viable, and consistent, therapeutic product. That is not say that scientists working in basic research do not use GMP, indeed they may be working with GMP approved cells and reagents and working towards producing a standardised protocol. The difference is in the freedom that these basic researchers are allowed (many of whom have never previously needed to work under full GMP conditions), as one member of the BloodPharma team explains:

> *"A big culture change… it's just how you work in a lab. Because in a research environment you can do, 'oh I'll try a little bit of that' or 'I'll add a little bit extra medium' for example, and it doesn't matter. Whereas in a GMP environment you have the protocol which has to be followed, and you have to note down absolutely every single thing that you use, from what plastic-ware, how many mls of media, what time things go into the incubator, what time they go out of the incubator. Every single thing that happens to your culture needs to be noted down, just whole control of what happens and you feel, coming from a research background, you feel you have very little freedom, we are building in more freedom into the procedures and that's been a learning process, how can we make the procedures flexible enough to do what we need to do but still comply with the GMP and traceability and records. So that's the way it's, for me, a big change from how you work."* (CS/Ind)

Here we see the balance that must be struck between the different working patterns employed by different team members. On the one hand allowing the researchers the

necessary flexibility to experiment, whilst on the other moving the process forward to the standardised protocol required to produce a licensed product. A period of free research allows development of the method which will eventually form these protocols. At some point it is necessary for these protocols to become 'locked-down', at which point the reagents have been approved and the protocol becomes the Standard Operating Procedure (SOP) which is followed by all the research sites. Although the SOP can be changed if necessary this lock-down prevents the constant tweaking which could otherwise carry on indefinitely and ensures that all the researchers are working to the same protocol. It can be speculated that this 'locking-down' of protocols may have some parallels with the discourse on innovation 'lock-in'. Liebowitz et al. (1995) discuss path-dependence, the idea that technology innovation often follows a path that is difficult to deviate from, even when this path is later found not to be optimal. Non-optimal technology might be seen as 'locked-in' to a path, because it would be too costly to change this technology. The QWERTY keyboard is often used as an example; the arrangement of keys is not optimal but the time and expense of changing keyboards and re-training users makes changing to better technology difficult. It is possible that the same problem could arise in locking down research protocols, that by the time it is discovered that the protocol used is not optimal the cost of changing the path is prohibitive. It is perhaps too early to tell if this is the case with stem cell therapies and problems may only come to light many years down the line. For now it is clear that manufacturing will require consistency as well as quality, and these GMP protocols allow the team to produce consistent outcomes across a range of research sites.

Given the different disciplinary backgrounds present within the team the issues of expertise were invariably raised throughout the project. The 'GMP-ing' of protocols was left to those who had experience in the translation of these protocols from laboratory to SOPs. The topic of expertise was seen especially in the approach of the researchers towards regulatory concerns. The attitude of the researchers towards the area of regulation was something which I specifically asked about in the interviews, and most of the comments articulated this idea of an 'expert', who took care of regulatory affairs so that others did not have to.

> *"Yeah, that's why this is good that, I know that, X deals with that, it's not my area of expertise. [..] And that is where X comes in and knows, and that were we can sit back and say 'well that's fine, we know that will be dealt with appropriately' and we don't actually have to be too concerned about it ourselves. [...] Because you can only be an expert in a certain area and it's a huge area, it's a whole area of expertise, let's face it isn't it."* (CS/Lab)

> *"You shouldn't have to be looking at regulatory, that's why you should have someone like me, that I can advise, because it's a full time job and you can't be expert at everything."* (CS/Reg)

The scientists appeared to be happy to leave the regulatory concerns to others in the team, in a way which did not seem the case for other key areas of the project. This dividing up of the regulatory process will be discussed further in Chapter Five. Indeed in all other areas emphasis was on the need to gain a good knowledge of the entire research process. This differentiation could be due to a number of factors, most prominently that the scientific research is a coming together of different disciplines which are all dependent on each other. Therefore there is a greater incentive to understand another person's work because it may help or hinder something which you also are struggling with. In contrast the regulatory areas can be seen as set apart, something which the researchers have no need to engage with as long as they follow the directions given by those who act as a bridge between the scientists and the regulators. It is of course also possible that this distinction between the regulatory and the scientific is an artefact of the data collection methods used, that misunderstandings between different areas of the scientific work only came to light in meetings which I was not allowed to attend. This struggle for each team member to understand the wider project shows that what is really needed in the future are more people trained in different disciplines, who can bridge the gap between the different areas of scientific research, medical and regulatory.

> *"I think the one thing we're missing all round, which is going to have an impact, is knowledgeable people in management positions. So, OK there's a lot of good scientists but people with, for instance X's awareness of the regulatory and the clinical and the science are very rare. And then the project managers, the regulatory managers with specific stem cell knowledge, you were asking whether the regulators had that but I think even the next step down, the people that are trying to prepare the paperwork are not there. I think we're missing a tranche of staff at the moment that need somehow to be trained."* (CS/Lab)

Highly skilled and trained staff that can interact with different areas of research are clearly seen as the future of scientific work, especially in assisting the translation of therapies from laboratory to hospital bed. Stem cells are highly specialised tissues and the development of therapies will require people trained in lab work, but who also understand the manufacturing and regulatory issues. This convergence of expertise is something which sets the BloodPharma project apart and leads it to be a 'paradigm shifting' project.

This section has detailed the importance of expertise and experience that have combined in the BloodPharma project through the work of a mixed team. Considering the three categories of knowledge creation outlined at the beginning of this section my evidence points to interdisciplinary working as the approach which best characterises knowledge creation within the BloodPharma study. The quotations reveal the importance placed on the bringing together of researchers from different disciplines in the pursuit of a common goal. It is possible to discount multidisciplinary working, as the BloodPharma case study brings teams together in a collaborative way to produce knowledge which is more than just the individual inputs. This is articulated by the respondent who talks about the project being a 'bigger thing', with all the groups requiring the knowledge and expertise that is held by other members of the project team. This emphasis on the disciplinary backgrounds and expertise of the different team members therefore means that the third option of knowledge creation, transdisciplinary, is not applicable in this case.

Although working collaboratively the team are still focused on the backgrounds which their discipline can bring to the larger project and have not fulfilled the transdisciplinary requirement for moving beyond disciplines altogether. It can be seen that translating early stage laboratory protocols into the GMP protocols required for industrial production requires knowledge in a range of areas. In the BloodPharma project this is possible because of the large team that has been brought together. The interdisciplinary knowledge creation has relied on many people, with specific expertise in a small area, contributing to the larger project goals. An interdisciplinary team constructed of researchers with a high degree of expertise in their chosen field

can bring potential problems in the form of tacit knowledge. The importance of this tacit knowledge in the culturing of stem cells will be discussed in the next section.

THE ROLE OF TACIT KNOWLEDGE IN EARLY STAGE LABORATORY PRACTICES

Stem cells are volatile tissues which require skill in control and manipulation, as well as in regulatory and manufacturing concerns, to develop a useable product. The previous section identified how experience and expertise are vital to the work of the team, attributes which are especially important when working with stem cells due to the large amount of tacit knowledge used in basic research. This section will explore the types of tacit knowledge used by the BloodPharma team, and how this impacts on the translation of basic science to future therapies. In the field of stem cell research tacit knowledge is seen as contributing to the ability of researchers to grow cells which, by their very nature, are unpredictable. The unpredictability of working with such tissues is a contrast to traditional pharmaceutical company products, which are in the main chemical compounds.

The role of tacit knowledge is becoming more prominent as traditional pharmaceutical companies move into the area of biologics (Wong, 2009) and tissue based therapies (McKernan, McNeish et al., 2010). Tacit knowledge is considered to be knowledge that must be gained through personal experience, the opposite of codified knowledge which can be written down or distributed through some form of media (Busch, 2008, pg.3). Collins (1974) argued that communities of scientists are distinct from each other because each community shares within it large amounts of tacit knowledge. This knowledge was difficult to convey through journal articles or presentations, and so it could only be shared by people who worked in close association with one another. Collins saw that knowledge diffusion between laboratories required not just phone-calls and written information, but also visits and staff exchanges. In many cases information transfer alone was not enough for another team to be able to replicate an experiment, the missing tacit knowledge was crucial. This idea of crucial tacit knowledge is repeated in Collins' later paper (Collins, 2001) on the measurement of the quality factor of sapphire. Experimental results achieved

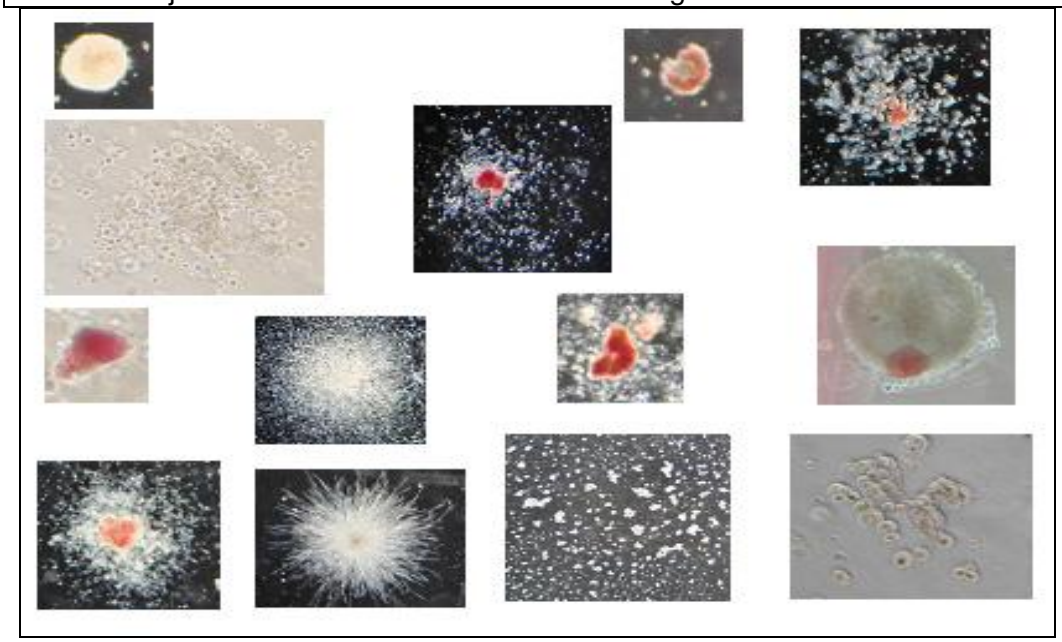
in Russia were not replicated until twenty years later, due to the important tacit knowledge missing from the original journal articles.

Case study methods are an ideal way of identifying knowledge transfer within a particular organisation, providing examples of how tacit knowledge is acquired and what happens if crucial tacit knowledge is not transmitted. The use of tacit knowledge in the BloodPharma project is related both to physical handling of the cells and also to observation. Examples of this observation will be used to demonstrate some of the laboratory challenges related to tacit knowledge. As stated earlier the laboratory work must be translated into standard protocols and so I will focus on the difficulties associated with that transition. Tacit knowledge is an important concept in stem cell science because of the nature of working with living tissue. Stem cells, by their very definition, are extremely volatile. Capable of differentiating into many different cell types the struggle is not simply to differentiate them, but to get them to differentiate into the cell type that is required. Standardising for uncertainty in the field of stem cell research has proven difficult to implement at laboratory level, with many research groups developing 'local' conditions to produce the best cell growth within a specific laboratory as standardised conditions produce inadequate results (Webster et al., 2008).

The reason for this push towards standardisation is that currently different methods are used to ascertain the 'potency' of a stem cell line. Such examples of uncertainty make it difficult to exchange research findings across a field, and so calls are being made for increased standardisation of stem cell research (Eriksson et al., 2008). Tacit knowledge is also commonly acknowledged within the stem cell community, as I discovered when talking to scientists or from conference presentations. People talk of laboratory workers being 'green fingered', able to grow cells when others could not, or of incidences where shaking a bottle the wrong way resulted in failed experiments. These appear to be explicit accounts of tacit knowledge at work. The visualisation of research processes is an important tool in describing these techniques to others and attempting to overcome the tacit knowledge gaps between different laboratories.

Images and visualisation are important tools in the early stage development of the

Figure 2: Cell colonies
Visual identification of haematopoietic cell colonies during differentiation, to be used in conjunction with the flow chart shown in Figure 3.



cultured blood project and here I will concentrate on the use of images for visualisation of biological process in the laboratory, and images as they are used in discussions by the team, e.g. in presentations. Imaging and visualisation have always played an important role in laboratory work, but this is often focused on how scientists visualise items that are invisible to the naked eye. How to ascertain that instruments were recording the 'truth' gave rise to the idea of the 'experimenter's regress' proposed by Collins (1992). As visual identification techniques such as electron microscopy become accepted methodologies in their own right the problems of validity diminish as the instruments become trusted (Ruivenkamp and Rip, 2010). Instead focus turned to which methods were most reliable for visualising the imperceptible, and to how these methods become accepted within a scientific community.

Visual inspection is a key part of certain processes during this early stage laboratory work. For chemical compounds it is normally possible to have set timings and temperatures for every step of the process; however this is more difficult for experimentation that involves living tissue. Cells may grow faster or slower than

expected and so steps in the protocol require the researchers to make a judgement, by eye, of how well the cells are growing and which colonies of cells they should be taking forward in the process. Visual identification is therefore used to separate mixed batches of cells, to check whether cells are growing correctly or are at the right growth stage for the process to continue. Visual identification requires expertise and practise and the ability to conduct certain visual identifications is often knowledge that is shared within one laboratory, or between a few of the team members.

This expertise implies that there is a certain element of tacit knowledge associated with making such identifications. Whilst it is true that practice and learning in the laboratory accounts for a much higher speed and accuracy it is also the case that attempts have been made to codify this visualisation process. Pictures are used not just in training but were also displayed in the lab to give researchers a method of

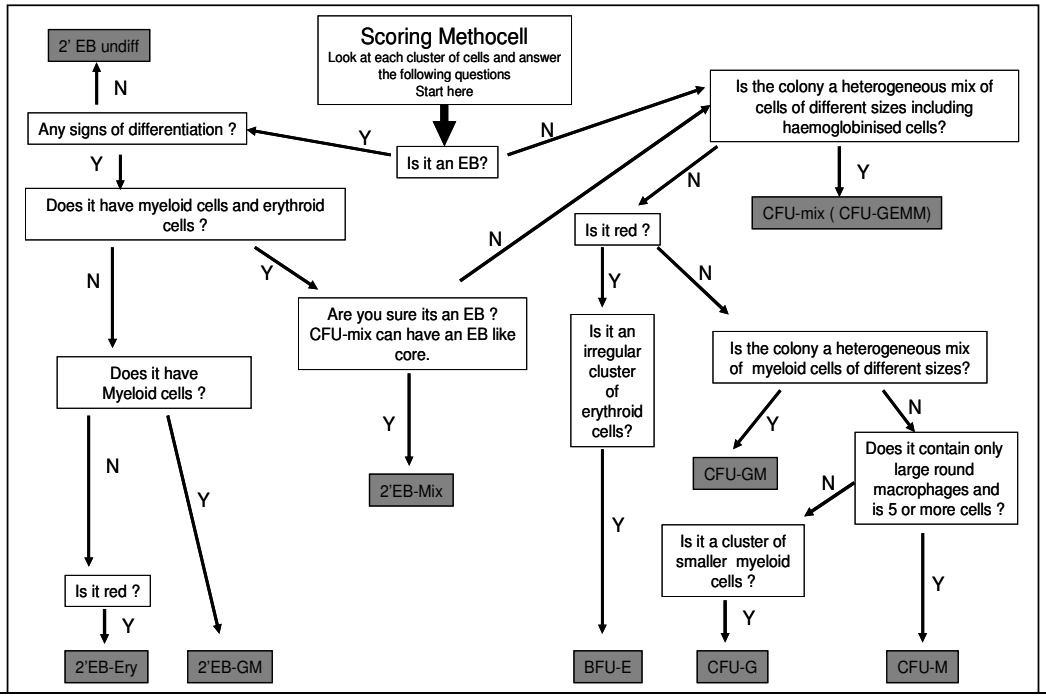


Figure 3: Identifying Cell Colonies
Flowchart showing the different steps in the visual process to identify different types of cell colonies, a flowchart made to assist identification using a microscope and showing the expertise required to make judgements at each stage of the process. Diagram reproduced with acknowledgement to the BloodPhama team.

visual comparison. The images in Figure 2 and 3 are taken from a PowerPoint

presentation designed by a member of the team to teach new laboratory staff how to visually identify different types of haematopoietic colonies during cell culture, using a microscope. This picture in Figure 2 is also displayed next to the microscope in the lab and is accompanied by the identification flowchart shown in Figure 3. The fluffy white object, second from left in the bottom row in Figure 2, is actually a bacterial colony. It is included as a 'trick' after an incident where a student team member believed that they were obtaining lots of good embryoid bodies (clumps of cells formed at early stages of growth), but had in fact been counting balls of mould. It appears that what the rest of the team would consider were obvious differences between cells and bacterial colonies were not apparent to the new member of staff who had little experience in the visual identification. A mistake such as this had subsequently prompted the team to highlight these distinctions in their training information. Here we can see that tacit knowledge is not just important in the physical processes of handling laboratory experiments but also plays a crucial role in mental decision making and identification.

Tacit knowledge is considered to be shared between teams that work closely together (Collins, 2001), and the BloodPharma project is no exception to this. Due to the nature of the wider project grouping there are researchers who share close working environments and similar expertise, but who also interact on a regular (but not daily) basis with other researchers, all of whom are working towards a common goal. Visual representations of research therefore become an important tool for explanation, especially as many of these wider group meetings take place away from the laboratory. The visualisation of the RBC has also been prominent throughout the project. As will be discussed further in the next section the team have used the human body as a benchmark throughout the project. The RBC has therefore come to represent the image of the ideal goal towards which the team are striving, in similarity to Lösch's (2006) case study of visionary images as communication in the nanotechnology sector. RBCs are highly recognisable and much of the literature used in public outreach by the team has featured pictures of RBCs, alongside visual props such blood donation bags filled with 'blood' (for health and safety reasons actually made with glycerol and food colouring). This visualisation of a RBC demonstrates

how the BloodPharma project team is seeking to create something which already exists in nature. They are not chasing after a new, imagined, drug or compound but are instead attempting to reverse engineer something which the body produces with little trouble. The frustration is that whilst RBCs are produced with apparent ease by the body, the processes which produce them are extremely difficult to replicate in the laboratory. On one occasion a subset of team members were presenting visual data of RBCs, referring to them as 'doughnuts' or 'bagels', to differentiate what was clearly an important difference visual between the two. I was unable to see any difference in the pictures shown and the person sitting next to me admitted the same. This differentiation was clearly only visible to those who were trained to spot it, and therefore a clear example of the expertise and tacit knowledge that existed within the different laboratory teams, but not between them. The copyright of these pictures has been assigned so I am unable to reproduce them here, however see Figure 2 in Griffiths et al. (2012) for an example of the RBC visualisation often presented by the team.

The importance of pictures in explanations is becoming more apparent in latter stages of the project where different fields of expertise are being brought together. Rose (2012, pg.13) writes it is not simply the images used which are important, but who is viewing those images. The biological team has now been joined by physicists and biochemical engineers who will work on the next stages of the project (the subject of Chapter Four). The team is therefore faced with having to explain its work to others who may have no understanding at all of the area of expertise. I noted at recent meetings that the biologists often use quite complicated explanations, an example of which is shown in Figure 4, as if assuming that all those in the room have at least some understanding of the diagrams they are presenting. In contrast the engineers and physicists use very simple explanations (Figure 5), even using everyday objects to represent complex processes. Their reasoning for this was that they always assume nobody understands what they are attempting to explain. The pictures used here are attempting to visualise the thoughts that the researchers have, and we are reminded

of the difficulty of explaining cognitive thoughts as discussed by Nersessian (2004), who acknowledges the difficulty of explaining a thought process that is not only highly individual, but is also shaped by 'social, cultural and material aspects of

Figure 4: Scientific explanations by biologists
This picture was used by member of the scientific team to explain the action of small molecules on cell surface receptors. The diagram uses standard annotation to represent the two membranes and the receptors which sit within them. The arrows represent modes of action of proteins. Although this diagram has a standard layout it requires a reasonable level of education in a biological science to understand.

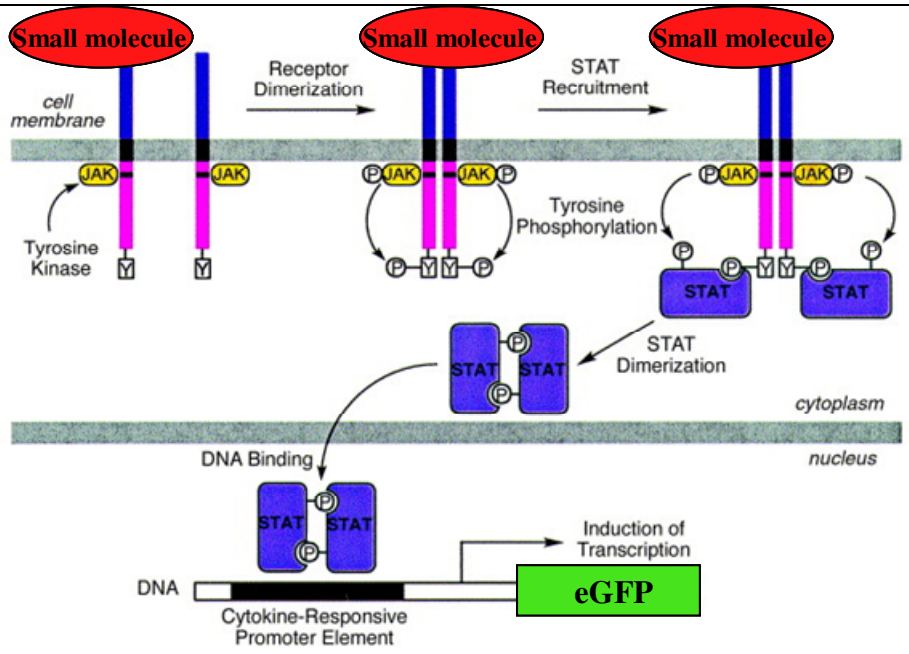
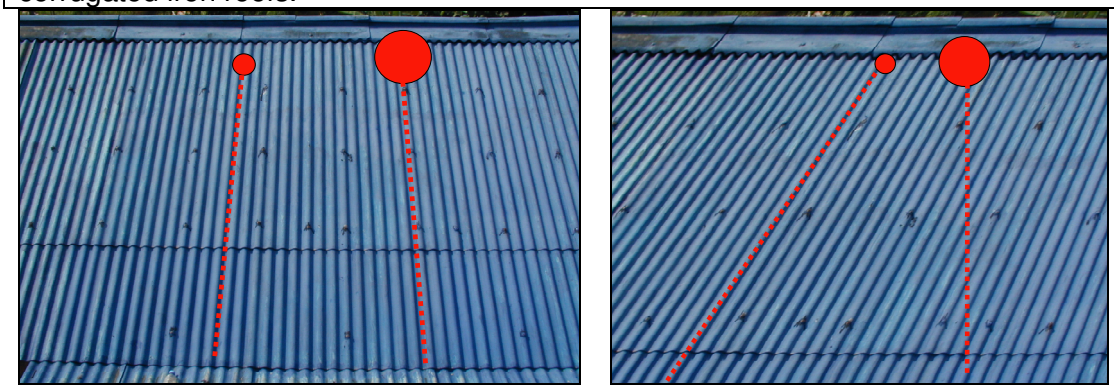


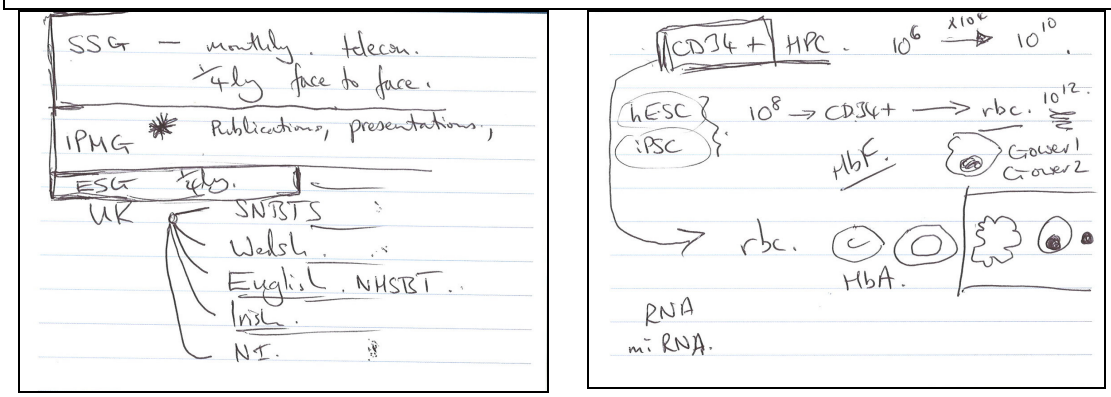
Figure 5: Scientific explanation by physicists
In contrast to the picture above these two diagrams are typical of those used by the physicists in the team to explain the complex methods behind cell sorting technology. They clearly show the effort to simplify their explanation so that everybody in the group can understand. In this case using the example of balls running down corrugated iron roofs.



practice'. Coincidentally the subject of her case study was a laboratory growing artificial blood vessels, in which those with engineering backgrounds also sought biological knowledge on an 'as needed' basis.

PowerPoint presentations have been the standard way in which data is formally presented and explained to members of the different laboratories in a wider group setting. It has also been noted that the researchers draw or doodle on a regular basis, especially when in a smaller group setting. These drawings occurred on the back of pieces of paper, on napkins during conference dinners, in the margins of slide handouts etc. The act of drawing was rarely in order to show the drawing to others, instead they seemed to be a way of the speaker collecting their thoughts or of sketching out biological processes to see if a certain suggestion held possibilities. The lack of examples available to present here to the reader was due to the propensity of the researchers to tear them up or throw them away immediately after they had finished drawing. I can only speculate as to why the researchers used

Figure 6: Informal drawings
Two informal drawings by one of the project team. On the left detailing the make-up of the blood donation system in the UK. On the right the production of cultured RBCs. Note the representations of different RBCs on the right hand side.



drawing to visualise their work, but I will propose that it is a way for them to collect their thoughts in the absence of a laboratory. The complex processes with which they work had to be distilled in some way so that they could check that nothing had been missed in their explanation. In the laboratory, when talking to me for example, they could point at screens or show me images down the microscope. Outside the laboratory this was not possible and so they resorted to drawing cells and doing

calculations on paper instead. These explanations were never 'for' me (the example in Figure 6 is the only one that I was able to retain) but they seemed to act as a way for the researchers to ground their explanations.

The possibility of this mis-identification occurring through the use of visual identification highlights some of the problems with tacit knowledge in the context of manufacturing these therapies on a larger scale. The important consideration of GMP, which requires very specific protocols, does not lend itself well to necessities of observation and decision required in stem cell growth. There comes a time when the working protocol must be locked-down to the SOP protocol which can then be distributed to the other laboratories to ensure that all staff are working to a consistent method.

> *"And that translation process really starts with getting the protocols from the researchers and that can be either something on the back of an envelope or it can be something with numbered pages and a title and approved."* (CS/Ind)

This idea of the 'back of an envelope' protocol reflects some of the spontaneity and trial-and-error that exists in laboratory work. The majority of experiments are carefully planned, written-up in the appropriate method in laboratory books and signed off accordingly. There still, however, exist 'eureka' moments, where plans are scribbled on napkins during conference dinners or quick calculations are written on work benches. This trial and error represents a constant striving to make the process as 'good' as possible, be that more efficient, quicker, cheaper (or most likely all of these). Protocols could be tweaked almost indefinitely:

> *"It's never something that "this is something we've now taken as far as we think we can go, it works nicely, here's the process a, b, c and well off you go."* (CS/Ind)

Researchers can become extremely attached to the protocols that they have designed and trialled over a long period of time, and it must be difficult to stop improving the method and hand it over to be standardised. This close interaction between the staff and their protocols could be considered the basis for why tacit knowledge plays such an important role in the translation of these working methods. Immersed on a daily

basis in the protocols that they designed it is easy to miss the small but crucial steps that they perform, and have perhaps missed recording in the written protocol:

> *"Or just something you, you just do it 'like that'."* (CS/Ind)

Once these protocols are taken away and eventually passed to other researchers they may find that the original results are not replicable. It is the challenge of those translating these protocols to uncover why the method used by one researcher cannot be repeated successfully by another, as this conversation shows:

> *"A: "Oh I always reverse pipette at that stage" something simple like that can have a big impact on dilutions or the way things are done, so. Often with cells I think there's a lot of, we're still at the stage where it's still down the microscope observing these, the critical decisions are made through observation. So actually the person doing that, if you've got somebody in a research lab who's doing that for three or four years, and that you hand it to somebody else and they can't replicate it.*
> *B: You have to have your eye in for the right, what they're supposed to look like, and that is the thing that's hard to translate.*
> *A: But I think it's engaging early and being able to identify those bits of in-house knowledge that people have and identifying those reagents that are likely to cause issues down the line and tackling that early."* (CS/Ind)

As we saw earlier the visual identification of cells is extremely important, and requires a lot of training in order to get right. Members of the team occasionally spend time in each other's laboratories in order to be able to replicate the protocols which are being used (an example of Collins' (2001) 'staff exchange'). In later stages of the project the team has been calling for a secure online file store that can be accessed by all team members across the country, primarily so that protocols can be accessed and discussed between team members.

Tacit knowledge is so important because researchers are attempting to gain control over cells which, by their very nature, could potentially differentiate into many different types of cell. The researchers have to 'persuade' the cells to think that they are blood, and to think that they are blood inside a person who has been born and is breathing outside the womb (in the case of the switch from foetal to adult haemoglobin, which is explained below). This manipulation of cells can be seen as an excellent example of the experimental intervention that is discussed by Radder (2009), who talks of scientists producing new objects through their intervention in

the material world. What distinguishes this intervention as an experiment is the level of control and discipline over the environment and the experimental process, as well as an element of reproducibility (Radder, 2009). Collins (1975) uses the idea of reproducibility to study knowledge transfer between scientists, which again returns to the importance of tacit knowledge in the replicability of scientific experimentations. Whereas some areas of experimentation allow control to be so defined that proceeding experiments can be considered identical replications (Radder, 2009), this clearly does not apply to the manipulation of living tissues with all its attendant inconsistencies. This control that the scientists must gain over nature leads us on to the next section, which discusses some of the issues around naturalness/unnaturalness associated with RBCs, as well as the use of the body as an exemplar by the researchers.

THE ROLE OF THE NATURAL/SYNTHETIC DISTINCTION AND OF THE HUMAN BODY AS AN EXEMPLAR

The previous section discussed the tacit knowledge that is required in the production of stem cell therapies, due to the fact that stem cells require large amounts of experience and expertise to control. This section will continue to discuss how the team has attempted to use stem cells to produce the tissues that are required, by using the human body as a template or exemplar. It will also discuss whether trying to mimic the human body is appropriate not just as a tool for research but also as a benchmark for regulation. Finally it will introduce the idea of naturalness/unnaturalness in the case of cultured RBCs, and discuss the importance of this distinction.

Stem cells are, depending on their level of potency, capable of producing some or all of the tissues in the body. In the human body they will be subjected to a vast range of physical and chemical cues which direct the differentiation of these cells. In the laboratory these cues are difficult to mimic, because the cues themselves are not well understood, or because the growth conditions and surrounding tissue found in the body are not present. In order to control and differentiate these tissues in the laboratory the team must look towards the one thing that is capable of this control,

the human body. The human body is used throughout the project as an exemplar, a benchmark of what the team should be aiming to replicate. The early attempts to create alternatives to donated blood had focused on chemical substitutes such as artificial oxygen carriers. Despite much effort and funding these alternatives never produced safe and effective therapies. As one interviewee pointed out the researchers then decided to look towards the human body and realised that the answer probably lay in the cells themselves.

> *"And it* [using chemical substitutes] *didn't work, and then that threw a bolt at us, why didn't it work? And then you think, well there's probably something wrong with it because nature doesn't have it in the raw, it's taken very great care to evolve a packaging system for this. […] So we are going to have to make cells. Something that looks like cells, either membrane encapsulated haemoglobin, which might still work."* (CS/Med)

Here we see a theme arising that 'nature knows best', recognising that the attempts to create free-form haemoglobin was a failure because the body had already worked out that this couldn't be done.

Throughout the project the team constantly look to the human body in attempting to improve the growth and maturation of the cells. It is challenging the pre-conceived idea that stem cells grown in culture require space and good gas supply in order to grow 'happily'. By looking to the human body it can be seen that haematopoietic stem cells give rise to RBCs inside the bone marrow, where they are densely packed and gas exchange is minimal. It is hypothesised that the cells may actually perform better if these conditions are replicated in the laboratory. The difficulty of getting RBCs to enucleate also demonstrates the difficulty in replicating RBC growth in-vitro. Mature RBCs contain no nucleus, but during development these cells do contain nuclear DNA and the nucleus is then lost through the process of enucleation. Enucleation literally expels the nucleus from the RBC, and the free nucleus is then destroyed by macrophages. Enucleation is visible down the microscope, but the signals that direct this process are still not well understood. Early stage RBCs taken from human donations and matured in the laboratory do enucleate, whilst the cultured RBCs appear to get very close to enucleating without completing the final steps. There is speculation therefore that some cues early on in the process of cell development are required for the RBCs to later enucleate. This is problematic as the

cells grown in culture are a homogenous population of developing RBCs and do not contain other cell types. If this unknown signal comes from the macrophages, for example, then the team will have to chemically mimic this signal or find another way to force the cells to enucleate.

A key theme throughout the BloodPharma project has been the use of the human body as an exemplar, as discussed above, coupled with the concept that cultured RBCs must look like *in vivo* RBCs. My data show that the BloodPharma team are anxious to distance the cultured blood product from previous technologies, such as synthetic blood products, GM crops, and gene therapies, which were not well accepted by the wider public. As for cultured RBCs we are discussing how a manufactured entity can be shown to be the same as something which already exists in nature it may be useful to look more to the area of genetically modified crops, and the use of 'substantial equivalence'. Millstone et al. (1999) write "if a GM food can be characterized as substantially equivalent to its 'natural' antecedent, it can be assumed to pose no new health risks and hence to be acceptable for commercial use". However it is uncertain if substantial equivalence would be an appropriate tool for assessing cultured red blood cells.

In the same paper Millstone et al. (1999) claim that substantial equivalence is nothing more than pseudo-science, a marketing ploy to satisfy biotechnology companies who want to prove that GM crops are safe, whilst setting safety barriers as low as possible. However published substantial equivalence studies, such as Baker et al. (2006) and Beale et al. (2008), show that a wide range of sophisticated laboratory tests are required to produce the results of this so-called 'pseudo science'. A more practical criticism is that the tests used to ascertain substantial equivalence cannot stand alone as a methodology because, whilst they identify differences between the natural and GM plants, they do not predict what effects (if any) these differences may cause (Kuiper, Kleter et al., 2002). Additional methods, such as toxicology and immunology testing, would be needed to establish the phenotypic differences between the two plant types. Miller (1999) expresses disbelief at the widely held conviction that, because the genes introduced into GM crops are known, this

therefore confers superior knowledge of the phenotypes of GM crops over natural crops. The criticisms of substantial equivalence tests have led to scientists and regulators calling for a move beyond the idea of substantial equivalence, to instead focus on safety and toxicology testing. This testing would bring GM crops in line with pharmaceuticals, pesticides and food additives, putting the focus on safety to the consumer rather than on proving that the GM crop shows substantial equivalence to the original variety (Schauzu, 2000).

The need to show that cultured RBCs have equivalent properties to *in vivo* RBCs also has parallels with the concept of 'bioequivalence' in generic drug manufacture. Once a named-brand drug is at the end of its patent life there is the opportunity for rival companies to develop a generic, and normally cheaper, version of the drug. This is permitted providing that they can show bioequivalence, that their generic version acts in the same way as the original drug (Meredith, 2003). Many companies specialise in creating generic drugs, for example the 1972 Patent Act introduced in India (which allows patents for production processes only on pharmaceuticals, food and agro-chemicals) opened up huge possibilities for R&D in generic drugs and in reverse engineering of pharmaceutical processes (Kale, 2010). Proving bioequivalence can be difficult and there are criticisms of the different methods used. For example Meredith (2003) highlights the problems of extrapolating from test subjects to the general population, whilst Hauck and Anderson (1994) and Fluchler et al. (1981) chart some of the varying formulas that can be used for measuring not just prescribability (the affect that the drug will have on a new patient) but switchability (the affect that the drug will have on a patient used to the named brand who is now switching to the generic). Although bioequivalence shows some useful parallels with cultured blood production it still refers to the equivalence between two man-made chemical based compounds, and the way in which these are proven to have the same action.

Whilst the team may use comparisons with previous technologies in order to understand the regulatory hurdles around the cultured red blood cells, neither substantial equivalence nor bioequivalence appear to be fully applicable to cultured

red blood cells. One reason is that bioequivalence and substantial equivalence are generally used as a way of justifying the requirement for less stringent regulation of the new product, whilst in the case of cultured RBCs this regulation will be unavoidable. Another point is that substantial equivalence focuses on equivalence in everything but the desired change, which is possible in areas such as genetic manipulation but not for cultured red blood cells, where such changes are less well defined. Similarly bioequivalence looks only for equivalence in function, without taking into account the underlying properties. However the BloodPharma team are interested in not just the functionality but also the genome of the cells prior to enucleation and the proteins present in the cells, as we shall see below,. Therefore it would appear that whilst functionality and underlying properties of the cells are both of interest, such comparisons are not fully met by drawing on the ideas of substantial equivalence and bioequivalence. The general comparison of the BloodPharma product with GM crops, although understandable, would also be well avoided lest the cultured red blood cells become caught up in a regulatory debate framed around the issues of GM crops. It is clear however that some form of 'equivalence' will be unavoidable in assessing the comparison with the current *in vivo* red blood cells, and to understand fully the issues of public acceptability, as will be discussed further below.

Despite the unsuitability of both bioequivalence and substantial equivalence in this case, the need to show likeness with *in vivo* RBCs has been a recurrent theme throughout the project, as the quote below illustrates.

> *"What they will have is an expectation that they perform physiologically the same. And in terms of the physical dimensions I assume that they will want them to be the same so that they can squash through the small capillaries, because otherwise you are going to get clots."* (CS/Reg)

This quote raises a number of points which the previous substantial equivalence literature addressed. The first is the comment that the cells need to 'perform physiologically the same', which appears to be a reference to both bioequivalence and substantial equivalence – i.e. this new product will be safe and effective if its performance is indistinguishable from the existing product. This reasoning seems sensible (as the second sentence of the quote explains) because if the cells are the

same size and the same shape then logically they can squeeze down the same capillaries as *in vivo* RBCs.

> *"If they didn't look and act the same, in terms of plasticity and stuff, then the regulators would ask you to justify that they won't cause a thromboembolism, that's.. I'm guessing that's what they would ask. Whereas if you could say, look that pint of blood down a microscope looks the same as that pint of blood down a microscope, then there's going to be an ease to that." (CS/Reg)*

It is the second half of the quote that brings in the interesting notion of the visual aspect, "if they didn't *look* the same" (emphasis mine). There is an assumption that looking the same implies that these cells will also act in the same way. We saw earlier that a criticism of substantial equivalence is that even detailed knowledge of the genetics of an organism cannot predict its phenotype or indeed its physiology. Surely then the physical appearance of a cell cannot be expected to accurately predict how it will work in the body.

And who is doing the looking? In the previous section on tacit knowledge we encountered the expertise and judgment calls which must go into making decisions based on visual aspects. Is it the regulators that are looking at these cells or somebody who is an experienced RBC researcher? In talking about the 'ease' of regulation the interviewee is not implying that the regulation will be easy, the team are fully aware of the difficulties of regulating this new product, but rather that there will be an advantage if they can show that cultured RBCs are identical to donated RBCs. This assumes that the regulators will be comparing cultured blood with *in vivo* blood, rather than taking the approach of regulating as if this were a new product. Donated blood is currently regulated by the MHRA under its own set of regulations (The Blood Safety and Quality Regulations 2005, which include components such as traceability, inspections of blood donation facilities, collection, processing and storage for both blood and blood products) whilst cultured RBCs are expected to be regulated as an Advanced Therapy Medicinal Product (ATMP). Clearly then the applicability of requiring cultured RBCs to show equivalence is unclear for the present, given that they will be regulated in different ways. It is likely that the issue will be resolved only by moving further through the regulatory

pathway. There is clearly more scope for discussion on the regulation of cultured RBCs, and this will be considered in more detail in the following two chapters.

In discussing the importance of cultured RBCs 'looking' visually the same as donated RBCs, the question should be raised about what exactly the team mean by 'looking the same as'. It is of course possible that by 'looking' they mean that these cells perform identically to donated RBCs in all of the barrages of tests that the team expect to put them through. The previous quote, however, uses the analogy of a microscope, which would show only visual data, so in this case it appears the interviewee is referring to 'looking the same' as being a visual comparison. I must also consider the potential that the team 'dumb down' information for me in an effort to be helpful and allow me to understand. Therefore their idea of 'looking' might extend beyond mere visual appearance and cover a multitude of other physiological testing, for example testing of how well different cells will deform to fit along small capillaries.

I think it is therefore helpful to use a concrete example of an instance where the team talk about the idea of similarity between cultured RBCs and donated RBCs. This example also illustrates the importance of the human body as an exemplar. The instance that I have chosen to discuss in more detail is the maturation of haemoglobin, from foetal haemoglobin to adult haemoglobin. This quote explains the process of haemoglobin maturation in the human body:

> *"Foetal blood, the blood you have circulating at the time of birth, it's not the same as adult blood, there is a subtle difference. The haemoglobin form is different, and it switches over immediately after birth. All sorts of things go on for reasons I cannot begin to imagine. [….] So you start to breathe, your circulation changes, things close in your heart. The different passageways [that are] open in your heart [in the womb] because you don't need your lungs, so the blood is all shunted right to left, at the moment of birth all those things start to happen. And your haemoglobin changes."* (CS/Med)

Haemoglobin is the oxygen carrying molecule present in RBCs and comes in two forms, foetal and adult. Foetal haemoglobin circulates in the body of the foetus before birth and this form of haemoglobin binds oxygen with a greater affinity than the adult form, allowing the foetus to maximise oxygen transfer from its mother's

bloodstream (Giardina, Scatena et al., 1993). After birth the foetal haemoglobin is gradually replaced by the adult form of haemoglobin, until it has reached its eventual level of <1% by the time the child is around two years of age (Thein and Menzel, 2009). This change is not irreversible and adults retain some ability to produce foetal haemoglobin. There are certain blood disorders in which this normal switch from foetal to adult haemoglobin levels does not occur and these disorders are clustered together under the term 'Heredity Persistence of Foetal Haemoglobin'. In normal, healthy, persons a persistence of foetal haemoglobin produces no major physiological effects (although it can be advantageous in those who also suffer from sickle cell anaemia[2]) (Conley, Weatherall et al., 1963).

Getting RBCs to produce adult haemoglobin is no small task. In the human body they will be interacting with various other tissues and subject to a vast range of biological cues from the body. In the Petri dish this is an entirely different matter, as the cells must be persuaded that they are in an adult human and not in a laboratory. The biological cues that give rise to this change are not well understood *in vivo*, so mimicking these in the laboratory will be a difficult task, with seemingly little advantage other than to show biological equivalence to the regulators. There seem to be few biological problems associated with foetal haemoglobin, as evidenced by those who continue to produce foetal levels throughout adulthood. However, the effort and research funding that the team are currently spending on making sure these cells mature in the laboratory would appear to be evidence that it believes the cultured RBCs have to exhibit mature haemoglobin. This then is an explicit example of the team striving to show substantial equivalence, using the human body as an exemplar, because it believes that this substantial equivalence will be required by regulators. It also highlights the necessity of specific testing, as (as far as I am aware) the presence of foetal or adult haemoglobin could not be identified through visual identification alone. This discussion of bioequivalence and substantial equivalence and their relationship to the development of cultured RBCs only arises because of the

[2] Normal haemoglobin molecules are composed of two pairs of protein subunits, known as alpha and beta, whilst foetal haemoglobin has slightly different subunits, alpha and gamma. The gene for sickle cell disease affects the beta subunits, which are not present in foetal haemoglobin, and therefore RBCs containing foetal haemoglobin do not sickle.

distinction between the *in vivo* RBCs and the cultured RBCs. This could be constructed as a difference between the 'natural' RBCs of the body and the 'unnatural' RBCs of the lab.

If we consider blood made within the human body to be 'natural', in that it is formed by nature without human intervention, then what should we consider cultured blood to be? And does this distinction matter? Cultured RBCs occupy a unique niche when considering questions of natural/unnatural. As mentioned in the previous section on substantial equivalence cultured RBCs can be seen to have many parallels with genetically modified crops, in that they are essentially a manipulated version of the natural product. The abiding worry with GM crops seems to be that they are *too* natural, able to potentially hybridise with wild variants and escape the control of their producers (Raybould and Gray, 1994; Stewart Jr, Halfhill et al., 2003). RBCs do not have the potential to 'escape' in this way, but are there other important reasons to distinguish between the natural and the manufactured?

Scientifically being able to distinguish between the *in vivo* and the cultured cells would have certain advantages, one of which is the prevention of doping in athletes. Blood transfusions (either autologous or allogeneic) can be used to give a competitor a boost of RBCs beyond their normal levels, leading to increased levels of haemoglobin, better oxygen uptake and therefore faster race times (Brien and Simon, 1987). RBC doping cannot be detected by standard urine samples, and relies on blood sampling to gauge whether the number of red cells and haemoglobin levels appear to be exceptionally high in particular individuals. Anti-doping organisations have already approached the BloodPharma team to see if its expert knowledge of blood can assist in identifying whether athletes are using donations to boost their haemoglobin levels before an event. These organisations are especially interested in changes that may occur to the RBCs, which would indicate that cells have recently been returned to the bloodstream. Haemoglobin-based oxygen carriers have also been used in doping and, like RBC transfusions, require the athletes to undergo blood tests as these doping methods cannot be detected using urine sampling (Ashenden, 2002) Doping is also becoming more sophisticated with the use of red cell

production stimulants such as EPO used to boost the athletes own red cell count (Jelkmann, 2007).

Although there are practical reasons for wanting to distinguish between *in vivo* and cultured RBCs, there is also the consideration of the natural/unnatural distinction, and there are two ways in which this distinction can be made. The first is the distinction between 'natural' donated blood and 'unnatural' cultured blood. The second is the distinction between 'natural' cultured blood and 'unnatural' artificial blood.

> *"Remember the pluripotential stem cell line itself is not something that you normally see in-vivo, it's an artefact…" (CS/Med)*

The stem cell line is an artefact, one that does not exist in the body, or in nature. This would indeed imply that the products of that stem cell line, in this case RBCs, are in some way unnatural. Although it would appear that cultured blood could be considered distinct from *in vivo* blood I was interested to note that in a conversation with some Jehovah's Witnesses[3] they articulated that they would not accept cultured blood. Although they will accept some chemical blood products they will not accept anything containing the main blood components, so in this case cultured RBCs were too 'natural', even though they did not come from a living donor.

However we contrast the cultured and *in vivo* RBCs they are still different versions of the same biological entity, much like the distinction between established and GM crops. The aim of the BloodPharma project has been to create RBCs which are as indistinguishable from the natural version as possible. This is then in stark contrast to chemical blood substitutes which are markedly different from either cultured or *in vivo* blood. In her book 'Purity and Danger' (1966) Mary Douglas raises questions that are also pertinent to the subject of naturalness in the case of cultured blood. Beliefs about uncleanliness and defilement demonstrate the deep-seated anxiety

[3] Jehovah's Witnesses interpret literally the Bible verse Deuteronomy 12:16 - "Only you shall not eat the blood; you shall pour it upon the earth as water" (King James Version 2000). They do not accept blood donations or any blood products made from red cells, white cells or platelets.

about bodily waste and certain body tissues. Douglas states that in modern society dirt can be considered as 'matter out of place', that something is 'unclean' because it contravenes the accepted system (Douglas, 1966 pg.44-45). Cultured blood could be said to contravene our accepted system. By being neither a synthetic chemical derivative nor a human donation it does not fit into either category with which we are familiar.

Cultured blood could be considered 'dirty' because of its unnaturalness and out-of-place-ness, but *in vivo* blood has historically been considered unclean. Douglas (1966) includes many examples of societies in which menstruating women are considered not just unclean but able to defile others by their touch. Blood donations in the USA were marked with the race of the donor to pacify white recipients who believed they would be defiled by receiving blood from a black donor (a practice that continued until the 1960's) (Starr, 1999, pg.109,169). More recently the HIV/AIDS and Hepatitis scares have led to blood being viewed as potentially unclean and contaminated. Whilst cultured blood could be considered unclean it is apparent that cleanliness is something that has rarely been attributed to natural blood. Using the human body as an exemplar may have implications if the cultured RBCs come to be viewed in some way as unclean or a substandard synthetic alternative. The scientific team does, however, have the distinction that the product it is aiming for already exists in nature. We see here then that instead of reliance on substantial or bio-equivalence we should turn instead to recognise the important of 'bio-social equivalence'. This is a sign that other forms of 'equivalence' are important in understanding the acceptability of the cultured blood product, as wil be discussed further in Chapter Six. This has implications for the foresight of the product, as the end product is more concrete than some innovation visions can be seen to be. For example in Fleck et al. (1990) the requirements for some sort of word processing technology were clear, but in the early stages the form that this technology would take was unclear. We shall see next how expectation contributes to the early stage laboratory development.

THE ROLE OF EXPECTATIONS IN THE DEVELOPMENT OF CULTURED BLOOD

Developing a product or technology over a long time frame necessitates some use of 'foresight', an imagined end goal towards which the developers are working. Although drawing here on ideas of foresight it should be clarified that the BloodPharma team was not engaged in formal foresight procedures, rather the foresight here refers to more informal anticipatory activities. In the BloodPharma project we see that such informal foresight is not limited to the product itself but also to a perceived notion of what the regulators will require from the product and the long-term expectations of the product itself. The choice to discuss some aspects of foresight here, before the following chapter on scale up, clinical trials and future markets, is a deliberate one. Introducing the imagined 'end product' early on in the thesis reflects the early stage at which foresight occurs in the scientific research. This section will address how foresight and expectations contribute to early stage laboratory work, starting with the choice of the project itself before discussing expectations of both funders and the project team, anticipation of regulatory concerns, and potential future markets.

Although the original funding call from DARPA initiated the bringing together of the BloodPharma team the decision to pursue cultured RBCs was directly influenced by the physiology of the RBCs themselves. It was considered that compared with many other stem cell therapies RBCs have distinctive properties that would make them easier to pass through the regulatory system, as this interviewee explains:

> *"And it's such a simple tissue, this is the thing, and I think this is why as a stem cell product it is ideal because it's a single cell type, it's administered IV, it's a short lived transplant so, it just seems like the ideal thing to reinvent. [..]And we can sterilise it, you can irradiate it at the end as well, you can clean it up as far as possible. And we know how to handle it and it's being done at the same volume already, it's just the manufacturing issues, the actual distribution and administration issues are all dealt with. So it seems like a no brainer, but that's with the rose tinted glasses on."* (CS/Lab)

Other stem cell products show increased levels of difficulty in administration of the stem cell therapy to the target site. Two recent stem cell trials include the ReNeuron stroke trial and the US Geron paralysis trial. The ReNeuron project aims to use stem

cells to repair damage caused to the brain tissue during a stroke, whilst the Geron trial sought to repair spinal cord tissue after paralysis. The Geron trial has since been abandoned, whilst the ReNeuron trial is still ongoing. These therapies, although the trials were initially only looking for safety, required the injection of stem cells directly into the brain and spinal cord of patients respectively. These are both complex operations and in comparison, the intravenous method of introducing cultured RBCs into the patient is inexpensive, easy and low risk.

The length of time of patient follow-up is also under discussion regarding stem cell therapies. For most stem cell therapies a long patient follow-up time is proposed due to the potential risk of tumorigenesis, which may take many years to become apparent. In comparison to other stem cell products RBCs are short lived, lasting only around 100 days. The length of patient follow-up appropriate for cultured RBCs is not yet clear. Fully developed RBCs are the only cell in the human body that do not contain a nucleus, meaning they do not pose the same risk of DNA transfer that is problematic for other types of stem cell derived tissue. This lack of DNA also means that cultured RBCs can be treated to remove pathogens, for example by using radiation, which is not possible with other tissue types. The irradiation step shows that RBCs also contradict Rayment and Williams' (2010, pg.997) statement that "viable cell- and tissue-based produces cannot undergo a terminal sterilization step, as is the case with other pharmaceuticals". RBCs have some unique advantages over other types of stem cell therapy and they are therefore perceived by researchers as a potentially unproblematic therapy to pass through the regulatory system. They also illustrate one of the major difficulties in regulating cell based therapies, that often blanket regulations are inappropriate in the face of therapies which are exceptions to the normal rules. More about the regulation of cultured RBCs and stem cell therapies in general will be discussed in Chapter Five.

The reason for an anticipated end product is primarily a pragmatic one, it would simply be impossible to direct multiple individuals and millions of pounds worth of funding without a definite research target. Indeed, it is recognised that expectations are crucial for mobilising funding (Borup et al., 2006). The criteria for obtaining

research funding also forces researchers to identify at an extremely early stage things such as target markets, potential patient groups, specific details about the eventual product etc. In many cases the extreme foresight required by funding bodies must occur before any of the basic laboratory research has started, or has even been proven to work, when the outcomes are still uncertain. Rappert (1999) presents the UK Foresight Programme as an attempt to overcome this uncertainty in innovation, whilst Anderson (1994) demonstrates that foresight could be seen as working against the nature of early stage research by attempting to engineer in certainty, which does not yet exist. This is similar to Williams' (2006) work on the compression of foresight, with early assessment of Ethical, Legal, and Social Implications (ELSI) leading to a linear vision of the technology trajectory. Whatever the impact of foresight on the autonomy of researchers the increasing disparity between the funding available and the number of proposed projects means funding agencies must apply some level of strategic forward planning, in order to fund projects seen as most beneficial to society and that demonstrate best value for money (Anderson, 1994). The Wellcome Trust, which has funded this stage of the cultured blood project, is seen to have taken a considerable risk funding such a large project, the outcomes of which are unclear. The sentiment expressed by the researchers is one of gratitude that the funding body was able to take that leap and fund the project despite the uncertainty. The risk taken by the Wellcome Trust in funding this project perhaps explains the stricter milestone-led method of funding. Using milestones allows the funder to keep closer control on the project outcomes and to check that the goals of the project are being met within a reasonable time frame. The criticisms of foresight in removing the autonomy of researchers are perhaps exacerbated by this milestone way of working, which not only sets out what the researchers must be achieving but gives a stricter time frame in which this must occur. On the positive side having milestones allows the researchers to concentrate on a subset of activities for a shorter time period, rather than constantly having to project their expectations to an end product that may be many years away.

The expectations of the researchers themselves are a key consideration throughout the project. Those working on the BloodPharma project not only have to engage with

a projected vision of an end product that may be many years away; they also face challenges of working in a diverse team. Each team member has their own expectations about the outcome of the project, and managing these expectations is key to coordinating the team as the project moves forward. Borup et al. (2006) call this the 'performative' nature of expectations, building mutual bonds and shared goals. The foresight employed by researchers during the case study appeared to be highly individualistic. Whilst the team presented a collective front to other academics, the public and potential funders there were underlying differences of opinions between members of the research teams. I do not wish to imply that the united front presented by the team was in any way disingenuous, simply that some appeared to look further into the future than others.

> *"I mean if I really want to speculate then I don't see it taking over blood transfusion ever actually. But I can see it being used to produce cells that could be used in specific circumstances."* (CS/Lab)

Another researcher also told me that they personally did not see the end goal as being the supply of blood to the transfusion service. Instead for them it was a research project in which they would dramatically advance knowledge and understanding of RBCs and how they develop in the body. In contrast many of the researchers did see the end goal as potential replacement of the blood transfusion service:

> *"Fifty year view I think it has to. I just think that the risks of donor based collection and transfusion services are as outdated now as giving person to person transfusions were in the early days. I think we have to move on."* (CS/Lab)

Although they did see this as a very long term view, with the aim of the current funding stream simply to be the first step on that ladder.

> *"It is to my mind that in the end of the three years we have a small amount of a product, that has been produced at a clinically acceptable grade, which would be able to go into a person if we were in the position to do so. […] But no, to my mind if we have a tube with 10 mls of blood in, 10 mls of packed red cells from ES, that were suitable to go into a patient, a person, that's my defined aim, very much."* (CS/Lab)

Understanding the different goals articulated by the researchers has only been possible through focusing on this case study and eliciting empirical data from a variety of actors over a long period of time. The united front which the team must present to funders and the public is difficult to unravel without this methodological

approach. Managing the expectations of a diverse team is an essential part of working in a mixed team (Bidault et al., 1994). Literature on interdisciplinarity often highlights the need for teams to produce a consensus, a shared view of the project which includes defining the project outcomes, a suitable methodology and appropriate theoretical perspectives (Frodeman, 2010). Whilst the BloodPharma team have undoubtedly reached a consensus as to the main project outcomes there is still retention of individual expectations about the project.

From inception and through basic research the future requirements of the regulators have been considered. If the cell lines are not derived to the appropriate standards then there is a fear that the development of the product may have to be repeated from scratch using approved methods. The team, therefore, have sought to go above and beyond the current requirements, in order to 'future proof' their research against any requirements that are later introduced.

> *"We would make small choices, so for example if there was a clinically used reagent available rather than a bog standard research grade one we would start with the clinical reagent, just to build in that extra."* (CS/Lab)

But they were also very clear that they wouldn't do something for the sake of the regulatory system that was not also academically viable:

> *"So no I don't think I would ever take a route purely because it was regulatorely more simple, if it wasn't scientifically screaming out as being the right route. […] If X were to say to us 'look guys, this is never going to be acceptable, there's no way you can use this reagent or this method, start again' then obviously we're going to have to listen to that. But given that at the moment a lot of the work is informing the regulation still it's not yet become an issue."* (CS/Lab)

This quote illustrates the difficulty of attempting to adhere to expected future concerns of the regulators, when the regulators themselves are also making decisions based on new scientific evidence that arises during the research. Indeed it became apparent that there is a fine line between foresight and 'second guessing'. When visiting the laboratories the researchers often told me that they were doing something 'because the regulators will want it'. When questioned further however it often became apparent that that dialogue had not yet been had with the regulators. This is

not to say that the researchers were wrong in their assumptions, simply that on occasion they were working to perceived regulatory conditions which had not yet been verified. As one interviewee said when the question was put to them-

> "*Aye, they shouldn't do that. That's why they have regulatory affairs people!"* (CS/Reg)

The eventual end use is an important future vision for any new innovation (Bidault et al., 1994) and we have seen that the imagined final target is used to coordinate both researcher effort and research council funding. We discussed above some of these expectations, with different individuals articulating a different envisaged goal for the project. These envisaged goals did not appear to be connected with the background of the individual, or with their status within the team (as a PI or a lab researcher for example). What, however, did differ with background experience was the expectations of how this product will be used – particularly referring to the proposed target populations. The choice of target populations will be discussed in greater detail in Chapter Four, but these populations are likely to be patients suffering from thalassemia or sickle cell disease. Cultured blood has the benefit of better blood-group matching and reduced side effects for patients such as these, who require regular blood transfusions. One member of the team with a medical background talked about his work with sickle cell disease in Ghana, where he had seen first hand the devastation that it caused.

> *"So anyway, we go there and wandering around Northern Ghana, where sickle cell disease is endemic, sort of where it began really, malaria is endemic. And every hospital "do you see many sickle cell patients?" – "oh no, we don't see any". Right. And "lots of carriers but we never see any sickle cell disease". Kids all die, and they don't resuscitate them. […] So one in four of the children die, children of a couple of carriers, and 2 in 4 are carriers and 1 in 4 gets malaria, sadly. So it's an awful gene*." (CS/Med)

The interviewee had gone to Ghana because he wanted to see first hand the effects that sickle cell disease has on a population where it is endemic. His reference to malaria is due to the connection between the sickle cell trait and the malaria parasite. Whilst having two copies of the sickle cell gene is generally fatal, having only one copy offers the individual protection against the malaria parasite, hence the prevalence of the gene in areas of high malarial infection (Aidoo et al., 2002). In

discussing future work the team often referred to sickle cell or thalassemia patients as potential target populations, the way they would benefit from the cultured blood product, and so on. It struck me, however, that on the one hand there are members of the team that are medics specialising in haematology and who have experienced first hand patients suffering from these diseases (both in the UK and abroad). In contrast there are research scientists, working towards the same goal but who have probably never met a sickle cell or thalassemia patient. Their closest contact may have been witnessing some misshapen RBCs under a microscope. Yet all the team appear to speak about the target populations in the same way, about how they see the benefits that their cultured red cells will bring to improving the lives of these patients.

It would seem as if the research scientists have 'borrowed' this insight from the medics, who perhaps in turn relay to the scientists what they have witnessed first hand of these patients. It is an interesting consideration that people from diverse backgrounds have been able, together, to form a cohesive view of the benefits to target populations, which all seem to believe with equal fervour. Borup et al. (2006) write that "expectations link technical and social issues" because expectations look to the future where the technology is in use, and is therefore bound up with social considerations. The imagined use in target populations shows this technical-social linkage in action. The expectation focuses not just on cultured RBCs that are suitable for use, it is also bound up with the vision that they will be used to help vulnerable populations where current treatments are less than perfect. Although the end goal may be to supply the whole blood transfusion service this is a 20 year vision, whilst the target populations are a much closer possibility. This is also a reason why the use of target populations is likely to be foremost in the researcher's minds.

This section of the chapter has discussed the importance of foresight and expectations in the early development of a stem cell therapy. We have seen that blood cells have unique properties which may give them certain regulatory advantages, but that the regulatory path is still unclear and that the researchers must 'second-guess' the regulators or go above and beyond what is expected in order to avoid future problems. There is an important distinction that can be drawn out,

however, between stem cell therapies and other potential innovations. The literature around foresight and expectations generally refers to a future vision of something that does not yet exist. With stem cell therapies (and to a certain extent with drugs and biologics) the end vision is very clear because these therapies are designed to mimic tissue which already exists in the body. As one interviewee commented - "it just seems like the ideal thing to reinvent". The end product here is very clear, as was discussed in the previous section on the exemplar, they have to look and act like *in vivo* RBCs. Although the route to this end product may still be unclear, and the eventual uses of the product uncertain, the team do benefit from having a clear vision of the end goal which can be shared by the whole team. Although this clear vision may assist in the co-ordination of a team who come from mixed backgrounds it can also be a burden. Where the end product is just a vision it is possible to change that vision as challenges come to light along the developmental pathway. This is not possible with the cultured blood project as its end goal is to mimic biological cells, there is no room for manoeuvre around this and anything short of substantial equivalence may mean that the project is halted before the therapy reaches the market.

CONCLUSION

This chapter has revealed how early stage laboratory work is achieved through interdisciplinary, multi-lab working, where standardisation of methods is difficult and where there exists an accepted technology. Themes of uncertainty, non-standardisation, and foresight feed into early stage laboratory work in the development of a stem cell therapy. The BloodPharma case study has shown how groups from different backgrounds carry out interdisciplinary knowledge creation under a funding model that is very different to standard laboratory working. We have seen how interdisciplinary working brings together groups with a diverse range of expertise and tacit knowledge to tackle such a large research challenge. Differences can be seen between basic scientists, who understand the biology of the cells, and clinicians who understand the clinical applications of such a therapy. There is also diversity between basic scientists and those with an industrial background, particularly in the translation of basic research into the protocols required for

translation. Despite differing areas of research the team work collaboratively, giving no impression that certain types of expertise are more important than other.

The importance of such expertise in the production of a stem cell therapy can be linked to the use of tacit knowledge in the stem cell field. We have seen that stem cells are volatile and unpredictable cells, requiring large amounts of control in order to direct to become the desired tissues. Much of the basic science requires visual processes, which in turn are dependent on the experience and expertise of the researchers. Examples of visual identification were presented here, showing the difficulties of identifying stages of cell growth and the charts which had been created to assist researchers in this process. The different presentation styles between the biologists and the physicists was also used as an example of visualisation within the project, as were the use of diagrams drawn by the researchers when discussing their work. The difficulty of standardising these 'back of an envelope' protocols into the standard operating procedures required for future work was discussed as one of the main challenges which tacit knowledge brings to basic research.

Throughout the case study we witness the importance of the RBCs themselves, and here we have seen their importance in relation to the use of the human body as an exemplar. The BloodPharma team occupy the unusual position of already having a viable product in blood donation, and therefore seek to mimic this *in vivo* blood in the laboratory. This use of an exemplar provides a target for which the team can aim, for example looking at the human body and trying to mimic the cues and conditions for RBC production in the laboratory. The use of bioequivalence and substantial equivalence was introduced, as they relate to pharmaceuticals and GM crops, and how they can also be seen to apply to cultured RBCs in this case. The use of equivalence was seen mainly to relate to an expectation of the regulatory system to see a cultured product which compared exactly with *in vivo* RBCs. However I introduced the use of foetal haemoglobin as an example of equivalence seemingly being placed above discussions about whether exact similarity matters in practice. The use of the human body as a benchmark led to discussions of the natural/unnaturalness of the cultured blood product. It was seen that there are a

variety of comparisons, between the 'natural' *in vivo* blood and 'unnatural' cultured blood, or between the 'natural' cultured blood and the 'synthetic' chemical blood substitutes. Whilst this distinction may not affect the regulation of the cultured blood product, we saw that questions of perceived cleanliness or 'matter out of place' could affect the uptake of a potential product.

Finally I have discussed the use of foresight in the BloodPharma project, which mimics the early stages at which the team themselves must look ahead to the eventual end product. Managing a consensus about the eventual end product is crucial to building such an interdisciplinary team, although we have seen that there are variations in expectations between team members about the eventual use of this end product. RBCs were shown to be an ideal target for research due to their easy administration and ability to be sterilised, in contrast to most other stem cell based therapies. Much of the foresight employed by the BloodPharma team referred to an expectation of the future regulatory requirements, using the best available reagents and GMP conditions for example, in order to convince the regulators of the provenance of the cells and avoid having to repeat any earlier work. Much of this regulatory foresight however had not been articulated by the regulators themselves but was an attempt by the researchers to anticipate future problems which they could tackle during the basic research stage. Scale-up and clinical trials require not just GMP quality research but also consistency, to take laboratory protocols and translate them into working protocol that will produce many litres of product. This is the next step towards a clinical trial of cultured blood, which is one of the many hurdles between the laboratory research discussed here and the future product.

CHAPTER 4: IMAGINING AND SHAPING FINAL PRODUCT AND FUTURE MARKETS

INTRODUCTION

The previous chapter discussed the early stage laboratory processes required in the development of cultured RBCs. At that point the team was still struggling with uncertainty around the enucleation and maturation of these RBCs. This chapter explores the anticipated processes and challenges once the enucleation and maturation hurdles have been overcome and the team is capable of creating small quantities of mature enucleated RBCs in the laboratory. I will focus specifically on the future challenges and opportunities of translating this emerging product into a viable clinical therapy.

The key question addressed in this chapter will be:
What does the Team see as the key challenges associated with translating cultured blood into a viable clinical product and how do these shape everyday practices?

Moving from laboratory scale to the vast volumes that would be required to replace the current donor blood transfusion service presents a number of unique challenges to the BloodPharma team. In the previous chapter we explored the important role that tacit knowledge plays in the production of stem cell therapies. Taking forward this 'hands-on' laboratory approach to a larger, and increasingly automated, production system presents significant and complex problems for the team to overcome. The already interdisciplinary team of the BloodPharma project will be further augmented by physicists and engineers whose skills and expertise are required to meet the long-term project goals. In this chapter we will follow the team members as they discuss potential routes through the primary hurdles of scale up, clinical trials and the identification of suitable target markets.

The first section of this chapter will look more closely at the scale-up which will be required to produce the cultured blood product. Scaling up the laboratory product to a level suitable not just for clinical trials but eventually for patient use presents many

challenges to the team, many of which are unique to the production of stem cell therapies and to cultured blood. To supply an entire transfusion service will require the development of specialised scale-up techniques and vessels. It is expected that it may require 20,000-25,000 litres of volume to produce 100 units of blood (a tiny proportion of the 2.2 million units required each year just in the UK), with the largest current bio-reactors in the world only holding 20,000L. The UK alone uses 2.2 million units of blood a year, leaving the team with an massive scale-up challenge. The first hurdle will be to supply enough product to be used in first-in-human clinical trials, although there is likely to be an additional requirement for pre-clinical animal studies, which will also require production of the cultured blood product.

Human clinical trials are recognised as a necessary safety measure in the development of any drug or therapy. For stem cells, however, the applicability of animal trials is not so clear cut and there is an ongoing debate about the efficacy of introducing human cells into animals. This second section of the chapter will present some of these considerations and the discussions concerning potential animal trials for the cultured blood product. Data from the BloodPharma team will be contrasted with interview data from another stem cell trial which is currently underway, and which is further down the regulatory pathway than the cultured blood project.

Assuming that the cultured blood product is shown to be safe and efficacious in clinical trials the next stage in the process will be the gradual introduction of the product to patients, which will be discussed in the final section. This is likely to start with the identification of small target groups who will benefit most from the cultured blood product. Potential target groups will be discussed here, as will future steps for introducing the BloodPharma product to a wider market. Throughout the project the team has discussed potential improvements that could be made to the product. These include making the product storable at room temperature, or using iPSC techniques to ensure better matching for patient groups. Some of these proposed advances will be presented, alongside the potential improvements that they could bring to the long-term introduction of cultured blood.

A key theme of the chapter is the unique challenges that are presented by stem cell therapies during this translation phase. These challenges are especially evident in the next two sections on scale-up and clinical trials.

THE CHALLENGE OF SCALE-UP AND AUTOMATION OF THE BLOODPHARMA PRODUCT

Translating the laboratory methods used to produce small quantities of RBCs into a large scale production process represents a major challenge of the BloodPharma project. Overcoming this hurdle requires the project team to consider new technologies and practices which may benefit this scale-up process. It is useful at this stage to consider the level of scale-up which will be required if the BloodPharma project were to make a significant impact on replacing donated blood. Every 500ml unit of blood contains around 2 trillion RBCs, and the UK requires 2.2 million of these units just to supply the current transfusion need (Mountford and Millican, 2011). Data obtained from the BloodPhama team show that they estimate it will require around 20-25,000L of manufacturing capacity for every 100 units of cultured blood produced. This is because in addition to the cells there is also a significant volume of media required, which contains food and other chemicals necessary for cell growth. In attempting to understand in real terms the volumes involved here I used these figures to make a rough estimate (around 6,000 units required per day in the UK, equating to 60 batches of 100 units each with each batch requiring up to 25,000L to produce) that it would require the same volume as four Olympic swimming pools to produce the cultured RBCs required for *one day* of transfusions in the UK. Clearly the scale-up required will be enormous and must represent a step-change in the technology used.

Indeed it is important to note that translating a method from the laboratory to industry is not simply a matter of repeating the laboratory process numerous times; rather there are additional factors of automation and standardisation which I will discuss in this section. A useful analogy used by one of the team members is that moving from the laboratory to industrial scale is similar to cooking a meal for two people and then having to cook for 200 people. Although the end result may be the

same the process involved is very different and requires something more akin to factory processes.

Since scaling up a stem cell product to the required volume necessitates something akin to a factory production process then we must consider two important requirements – automation and standardisation. Automation naturally leads to a high degree of standardisation, whilst the requirement for a standardised end product presupposes an automated process as the best method of production. As we saw in the previous chapter stem cell expansion requires a huge amount of tacit knowledge, experience, expertise and hands-on manipulation from the researchers. A degree of automation is the first step in reducing the requirement for large amounts of human resource which laboratory processes involve, and which makes laboratory work so consuming of both time and monetary resources. The constant and ongoing intervention currently required for most stem cell culturing has made stem cells a difficult prospect for processing in automated manufacturing plants which necessitate unvarying protocols (Placzek et al., 2009). In 2008 a workshop supported by the ESRC's Stem Cell Initiative brought together members of the regenerative medicine field to discuss the issues of automation in stem cell research. Their report raises key points such as the need for technology to link production steps that are currently semi-automated in order to reduce human intervention, and the importance of automation for standardising the stem cell field (Webster, 2008).

With increasing integration of research equipment and computer software the ability to automate certain processes is increasing. For example King et al. (2004) devised a robot capable of carrying out gene function experiments on yeast and generating further hypothesis based experiments. The robot needed minimal human intervention and was shown to be comparable with human researcher output. In their work on air pumps Collins and Kusch (1995) also comment on the progress made in automation over the preceding years, but highlight how much of the process, especially the setting up and troubleshooting, still requires human intervention. Whilst it may not be possible to make the production process for any product fully automated there are benefits in attempting to reduce the human intervention as much as possible. The aim

is not necessarily to remove the expenditure of employing staff, as it has been shown that the introduction of automation is not necessarily a cost cutting approach (for example integrated laboratory automated systems can have a payback period of 5-7 years (Mason and Hoare, 2006)). The real benefit of automation is in bringing increased standardisation to the manufacturing process. Automation removes the variation seen in culturing methods between different staff, and it could also remove variation between laboratories. The result would be the increased standardisation which is considered a goal by most of the stem cell research field. Shaw (2010) writes: *'When "the process is the product" — as would be the case with industrialized production of stem cells — variability is the enemy and must be reduced and controlled as completely as possible'*. The variability of stem cells grown across different laboratories is making it increasingly difficult to introduce an industry standard, especially as many labs employ what Shaw calls a 'whatever works' approach. The definition of 'pluripotency' is also under review as no standard test exists for measuring what is essentially a prediction of future ability to form different body tissues (Eriksson et al., 2008). Regulatory approval for a stem cell product is based on a product meeting certain requirements, for example cell potency assays, for which the licence was granted. Given the heterogeneity of stem cell populations, manufacturers will need to ensure that every subsequent batch of product meets these same criteria (Rayment et al., 2010).

Automation of the BloodPharma production processes requires significant changes to the biological protocol, which move beyond the design of machinery and software. A classic method of growing stem cells is to use 'feeder layers' comprised of mouse or human cells. Although these layers assist in the culture of stem cells they prove challenging for scale-up due to the large surface area which this method requires, relative to the amount of cells that can be produced (Xu, Inokuma et al., 2001). To increase the density of cell culture the most efficient method would be to use a tank of some kind, increasing the available space from a single horizontal layer to a three dimensional volume. This requires a method to be produced which allows the cells to be cultured without the use of feeder layers, as this interviewee explains:

> *"..also because it's [feeder layers] a contact based system the volumes that you need would never be suitable for conversion to full scale*

> *production. So we've been trying to engineer out that step, which is going very well, but at the same time we've introduced considerably more growth factors than we had before so the potential cost has gone through the roof but the ease has come down a lot, and it's going to be like that all the way through I think."* (CS/LAB)

As is revealed here, the downside to this method is the extra growth factors, which are required to force the cells down the correct developmental pathway without the assistance of the feeder layers. In addition alternative methods had to be found for parts of the process which are normally done by hand, for example the cell colonies growing in plates are normally cut apart by hand to allow for re-plating and expansion. The team has had to develop an alternative method that allows chemicals to be used to break apart colonies growing in suspension. Once a method for producing cells was developed that removed the need for surface attachment this allowed the team to move towards production in larger containers. Within the laboratory setting the team has started to develop techniques using containers with small volumes of liquid, for example two litre or five litre flasks. This volume may be enough for preliminary work to be carried out, for example characterisation of the product or animal studies, however my data show that the team expects batches of 1000 units to be required once Phase 2 or 3 clinical trials are reached.

The incentive to develop these automated techniques is not just due to the eventual need to scale-up to a vast volume of product, it is also to ensure that the product is produced in a standardised manner. Whilst the machines themselves can contribute to standardisation of research there is also standardisation required within and between the automated technologies. Without a standard use of barcodes, software, connectors etc. between machines the automation of an entire laboratory can be extremely problematic (Mason et al., 2006). One recent example within a local laboratory was the many hours of discussion that it took to convince the manufacturers of a particular piece of equipment that although the UK is technically in Europe it is common for UK laboratories to have imperial, not metric, connectors. The act of standardisation within and between the different machines and technologies is a small part of the wider task, which sees the building of routines within the team that are necessary for establishing a consistent method. This

consistency is vital because a small anomaly at the two litre level will be amplified if that protocol is then expanded to 20,000 litres. This consistency is the reason for the team's investment in a high level of protocol translation, with members of the team focused on identifying the correct reagents and on moving laboratory methods to a standardised and tested protocol. Whilst anomalies and mistakes will always take place within science the aim of these protocols is to engineer out potential for mistakes to occur. Star and Gerson (1987) talk of mistakes occurring, such as setting a dial incorrectly or the presence of 'funniness' within the experiment which cannot be accounted for. Such anomalies are considered normal within the laboratory experimental setting, but become a matter of importance when that is translated to an industrial process. The financial cost and the safety concerns of a mistake occurring in a 20,000 litre production vessel would have wide ranging implications. Star and Gerson (1987) used the example of cancer stem cell lines which were later found to be contaminated, throwing into question the results of many years of expensive research. Contamination is clearly a potential issue for the BloodPharma product, especially after scale-up when thousands of people will be transfused with the same product. My data shows that, although the team consider the possibility of contamination, the production procedure will be so controlled that they do not see this as a likely risk. Instead they consider that the risks already taken by transfusing patients with potentially contaminated donor blood to be considerably higher.

So far I have considered the benefits of automation on the production and standardisation of stem cell therapies. These benefits would be applicable to a small scale laboratory production process, however what sets the BloodPharma project apart is the difficulty of scaling those laboratory methods to a vast volume. Turning the method for producing *in vivo* RBCs from a small scale laboratory process into large scale production requires a shift in the use of technology and production methods. Through regular meetings with the BloodPharma team it is clear that scale-up has been a consideration from the beginning of the project, and is now (during 2012) becoming a major subject of discussion at most of the meetings and conference calls. It is important to bear in mind that at the time of writing the team is not yet able to produce the quantity of enucleated cells that would even be suitable

for clinical trial (i.e. a few millilitres), yet much time, effort and resources are being placed on the development of large scale manufacturing. This long timescale shows the challenge of scale-up of this type, as the team are aware that once the laboratory research is successful then the scale-up will need to be in place. It also is a measure of the confidence that both the team and the funders have in this project, and that cultured RBCs will one day be required in a large volume. The team has successfully managed the first step of the scale-up requirements, which has been to grow the cells in suspension, and without the use of feeder layers. This is a crucial step in allowing the product to be produced in some form of bio-reactor, without relying on cells attaching to a membrane (which would greatly increase the surface area required).

The next laboratory challenge is to find the elusive progenitor cell, which will allow the team to culture large quantities of RBCs without having to return to the original cell line each time. From the start of the project it has been expected that the only way to culture RBCs in the quantity needed would be to move towards the use of large-scale cell culture using bioreactors. There was an awareness of how difficult this would be to achieve, and that in all probability a new industry might arise from this, as these two quotes illustrate.

> *"Oh totally [use of bioreactors], and on a scale that's probably not thought of at the moment, the cell numbers are just frightening. But I do think it's doable but we're going to have to change a lot of thinking and a lot of systems, but why not?"* (CS/Lab)

> *"I think that to supply the country with cells there has to be a completely new company. With purpose built facilities I would have thought. It certainly won't be happening in our clean room!"* (CS/Lab)

In late 2011 the second phase of the project brought the team together with bio-engineers and physicists, who will be working on both scale-up and cell sorting techniques. Although the team had always spoken of the future requirement for bioreactors it was the introduction of these scale-up specialists that led to further discussions of the future practical challenges of large scale manufacture. The main challenges of cell growth being that as cells are living things they require nutrients,

gases, waste disposal and some level of protection. Bioreactors on this scale present physical challenges, especially in stirring the cells and ensuring that oxygen is allowed to reach all parts of the tank. The techniques required to build reactors on a large scale are not new, however many of the normal technology employed will have to be adapted if cells are to be grown in this way. One consideration is that tanks of this size require stirring in order to distribute nutrients and gases evenly throughout the mixture. Stirring using paddles is a well developed technique for most containers of this size, however living cells have very different properties from compounds such as cement, chemical mixes or beers, which are normally stirred in this way. Data presented by the engineers advising the BloodPharma team showed that they expect RBCs would simply be disintegrated by the force of the spinning paddle blades. Introducing air bubbles to disperse oxygen throughout the mix was also thought to potentially have an adverse effect on the cell growth.

Other considerations of manufacturing at such a large scale include separating the cells and removing waste media. Techniques such as centrifugation, which are used routinely in the laboratory on a small scale, pose a challenge for larger scale production. Even if machines could be developed which would cope with the weight of rotating thousands of litres of liquid they may still take many hours, or even days, to reach the revolutions per minute required, and to slow down again. Some of the considerations of scale-up and manufacturing are exclusive to the production of cultured RBCs. For example other stem cell therapies can be effective with very small numbers of cells, for example recent human clinical trials for macular degeneration involve the injection of just 50,000 cells (Schwartz, Hubschman et al., 2012). A unit of transfused blood contains two trillion cells, and due to the absence of a nucleus in RBCs there is also no likelihood that the cells will grow and multiply within the patient, so a smaller amount cannot be produced with the expectation of expansion *in vivo*. Although there is no alternative to the huge volumes which will be required there is some compensation. RBCs *in vivo* grow in the bone marrow, densely packed and with little oxygen. It is possible that this may be advantageous to the project as it may be possible that these cells do not required the same levels of oxygen that would be required for culturing other tissues. As we saw in the previous

chapter this is an example of the BloodPharma team looking to the human body as an exemplar.

Once the most appropriate scale-up methods for cultured blood have been identified the next step will be to consider how the infrastructure for long term production will look. The company with the largest mammalian cell culture capacity in the world is currently Lonza, which has 4 x 20,000L bioreactors situated at its site in Singapore. Although bioreactors on this scale are currently available (although these are stirred bioreactors, which may not be suitable for RBCs), to supply a worldwide demand of 100 million units a year, working on an estimate of 1 month per batch (100 units), would require 800 bioreactors of this scale. This is also based on an estimate of the current global usage of blood, where blood is both rationed to some extent in developed countries and completely unavailable in large parts of the world. It is likely then that the true production of cultured RBCs may be significantly higher than this prediction. Information from the BloodPharma team expects that:

> *"This level of scale-out of current technology after scale-up of the process is likely to require a step change in current manufacturing technology."* (CS/Lab) via email

It is still unclear exactly how the bioreactors will work on a large scale. Options include a batch process, where the reactors are emptied and cleaned between each batch of cells being produced, or a continuous process. If a continuous process is used then some form of cell sorting would be required to ensure that only cells at the correct stage are removed from the mix. There have already been questions raised around the cultured blood product about batch versus continuous manufacturing. It has been posed that continuously growing RBCs in large vessels and somehow siphoning off those cells that are ready for transplantation may cause regulatory concerns, as continuous processing does not allow individual batches to be identified. There has been some concern amongst the project team that the regulators will want to be able to track individual batches back to the point of manufacture in the event that future problems arise. Who is likely to produce this product also remains unclear, with my data showing that although the team hope the NHS can take the product production as far as possible there is an expectation assistance may be required from Big Pharma or other industries. Mason (2007) writes *'The production*

of large amounts of living human cellular material for therapy is at least one order of magnitude more difficult than that for biopharmaceutical applications'. Mason believes that the key to scaling up stem cell processes is for firms to collaborate with contract manufacturing organisations (CMOs), who already have experience growing mammalian cells in large volumes for the biologics industry (Mason et al., 2006; Mason, 2007). What is clear is that the BloodPharma project will have to continue building a set of laboratory routines which will result in the production of a product that can be expected to have consistent properties. They must struggle to overcome the inherent biological unknowns which are a factor of working in the regenerative medicine field and attempt to control biological processes to produce a product of both high quality and consistency. The first test of the product will be in the first stages of clinical trials, which will put the safety of the product at paramount importance.

UNCERTAINTIES IN THE CURRENT CLINICAL TRIAL REGIME AND THE DIFFICULTY OF PLANNING BLOODPHARMA CLINICAL TRIALS

Clinical trials for pharmaceutical products have been mandatory in both the UK and USA since the 1960's and there exists an established framework for the planning and conduct of these trials. More recently the development of both biologics based therapies and tissue based therapies have raised debate about the applicability of such trial designs for this new generation of therapies. The BloodPharma team is therefore negotiating a pathway through a regulatory system which still holds many uncertainties. Here I shall introduce some of the wider uncertainties around clinical trials, and the way in which these have been responded to by the BloodPharma team, before focusing down onto specific challenges associated with stem cells.

As the BloodPharma team is still at the early stages of developing a future clinical trial I will draw on data from another project, the ReNeuron stroke trial, which represents a stem cell product that is further down the regulatory route. ReNeuron is a UK based company which is seeking to develop a stem cell based therapy for the treatment of ischemic stroke patients. The therapy being developed involves the injection of stem cells directly into the brain of the patient. These cells are neural

stem cells, derived from tissue of foetal origin, and are known as the ReN001 cell line. The clinical trial is taking place in collaboration with the Institute of Neurological Sciences at the University of Glasgow, which is based at the Glasgow Western General Hospital, and incorporates a large Acute Stroke Unit. At the point of writing six patients have been treated with these cells, (covering the first two dose cohorts of a four cohort escalating dose study), no adverse effects have been reported and all the patients showed improvements in their neurological function. This data was published by ReNeuron on their website on 14th June 2012. As part of this thesis I interviewed a medic who was associated with the ReNeuron trial on two occasions, in June 2009 and again in October 2011. At the time of the first interview the company had gained MHRA approval for the trial but were still awaiting approval from GTAC. By the time of the follow-up interview the first cohort had been injected and the second, higher dose, cohort was starting imminently. Some of the challenges identified by the interviewee raise questions about the design and implementation of stem cell trials, which could be applicable both to the BloodPharma project and also to the stem cell field in general. At this point I shall concentrate on the design and implementation of the clinical trial itself, but further discussion about the interactions between ReNeuron and the regulatory authorities will be included in Chapter Five.

It has been proposed that 'clinical trials', in the form of comparisons of available techniques, have been in place since the time of the Egyptians. Evidence is scarce but it is considered probable that early societies who acquired sophisticated medical techniques must have employed some way of determining effective treatment regimes (Bull, 1951). Skipping forward a few millennia the study conducted by Lind in 1753 has become the landmark of more modern clinical trial history (Pocock, 1983). Lind was instrumental in discovering the link between citrus fruits and scurvy prevention after he conducted a trial in which different sailors were fed a variety of supplements, including (amongst other things) vinegar, nutmeg, and of course the all important oranges and lemons (Lind, 1753). The next landmark in the development of clinical trials considered by Pocock, which incidentally fits very well with the theme of this thesis, was a trial undertaken by Pierre-Charles-Alexander Louis. His instrumental trial in 1835 studied the use of bloodletting in patients and found there

to be no discernable difference between the treated and control groups, introducing the importance of untreated controls and strict observation of patient outcomes.

It was not, however, until 1927 when the first single blind study was used and 1950 before the first double-blind study was noted (Pocock, 1983). In a single blind study the volunteers do not know which treatment they have received, in a double blind study neither the volunteers nor the medical examiners know which treatment has been received. The Thalidomide crisis of 1961 called into question the way in which pharmaceutical products were released into the public domain, and as a result of this the UK established the Committee on Safety of Drugs to oversee pre-market clinical testing conducted by manufacturers. In 1968 the Medicines Act came into force, requiring government approval for human clinical trials and marketing of new pharmaceutical products (Abraham and Lewis, 2000).

Although clinical trials have been compulsory for the last 40 years this is not to imply that they have been without incident. Interview data from the BloodPharma team and the Re-Neuron medical personnel shows that adverse events in drug trials have made a lasting impact on the scientific community. Events recalled by the interviewees included the death of a volunteer in 1999 during an American clinical trial for retroviral therapy, the last straw for the area of gene therapy which had been struggling to achieve its expected results (Marshall, 1999). They also spoke of stem cell trials which took place during the 1990's and involved injecting bone marrow into patient's hearts and foetal tissue into patient's brains, with the hope of curing heart disease and Parkinson's disease respectively. Interviewees felt that these trials had been ethically dubious, for example the heart trials (which had used pre-clinical rat models) had been non-blinded, non-randomised and with no placebo control. The view was that as the product was autologous and minimally manipulated it was considered to be more akin to a transplant and bypassed many of the product regulations. One interviewee commented that the patients were treated like mice. My data shows that there is a real concern amongst the scientists interviewed that current stem cell research projects are conducted 'properly', and that the field is seen to

distance itself from the potentially un-ethical or dangerous trials which have occurred in the past.

Today clinical trials for pharmaceuticals consist of five recognised phases (Pocock, 1983; IDSD, 1991):

- *Toxicological Evaluation* – using animal models to determine toxic exposure levels, sometimes including effects on reproductive capability, tumerogenicity etc.
- *Phase I Studies* – First in human. To evaluate safety and dosage range before Phase II studies. Normally using healthy volunteers.
- *Phase II Studies* – Small scale studies in selected patient populations. Evaluates efficacy and determines effective dose.
- *Phase III Studies* – Evaluate safety and efficacy in a much larger patient population, many within a clinical setting.
- *Phase IV* – Postmarketing surveillance for reported adverse drug reactions.

This list represents a very brief overview of the complexities of conducting a clinical trial, but a common theme of all clinical trials is an attempt to replicate in the laboratory the effects of clinical pharmaceutical use. It is normal for trials to contain a control group who receive no treatment, whilst those who receive treatment are randomly assigned to receive either a placebo or the real product (Jadad, Moore et al., 1996).

Data obtained from pre-clinical studies in animals is currently considered to be a requirement for further human trials in pharmaceuticals and tissue based therapies, for example the EMA state that '*The objectives of the preclinical safety studies are to define pharmacological and toxicological effects not only prior to initiation of human studies but throughout clinical development*' (EMA, 2011). Frey-Vasconcells et al. (2012) provide a thorough overview of considerations that must be taken when deciding appropriate animal studies. Some key considerations are the number/type of animals necessary and whether a certain disease mimic is required. If testing of the full human dose is required is this possible in small animals or will large animal

studies be required? A common theme appears to be the lack of specific requirements as to the numbers/type of animal studies required, leaving it to the researchers either to prove that their animal studies are sufficient, or that there are no possible animal studies applicable. Whilst it would never be said that an animal could stand as complete substitute for a human there is debate over whether laboratory animals can even be seen as representative of their own species. Davies (2010), in her work on the applicability of mouse models in neuroscience studies, refers to 'nature implied', the idea that a mouse in the laboratory can stand as a proxy for the mouse species as a whole and also in some way for human behaviour. Lynch (1988) distinguishes between the 'naturalistic' animal, the animal as we expect it to behave free of human intervention, and the 'analytic' animal, an artefact and a tool for research which is shaped by human interactions. Hansen (2006) also considers the use of 'nature' or 'natural' rhetoric as drawing a distinction between what is outside the laboratory and what is inside.

Whilst the laboratory space can be seen as attempting to replicate the world outside in a condensed form Asdal (2008) also calls attention to the laboratory as a 'sub-place', a unique space in which certain practices (in this case vivisection) is acceptable in a way that it would not be in wider society. If we view clinical trials as attempting in some way to condense 'nature' into a laboratory setting then we see that the debates around the applicability of such trials generally focus on the distinctions between nature within and outside the laboratory. For example animals kept for research purposes often exhibit 'cage stereotypes' such as repetitive and functionless behaviours (Garner and Mason, 2002). Mice carrying certain genetic mutations are specifically bred in an attempt to model human diseases, with the aim being to simulate the progression of the 'real' disease under laboratory controlled conditions and over a reduced time period. Studies have shown that, in addition to cage behaviours, the behaviours and disease progression exhibited by these mice often varies between laboratories, meaning the results of experimental studies may be specific to a particular research group (Crabbe, Wahlsten et al., 1999).

Kaleuff et al. (2007) also provide a long list of potential problems with mouse models and their inability to accurately model the courses of disease in human, including the difficulty of modelling multi-factorial human disease and of over-stimulation by the environment. Oyston and Robinson (2012) report that in their area of vaccine development Phase II trials are often disappointing, as positive results found in early animal studies are shown not to be replicable in later human trials. In these cases the mouse is often used as a test subject, despite having a significantly different immune system from a human.

Differences in pharmaceutical trials are often reported due to the different ways in which drugs are metabolised in different animals. A pharmacokinetic profile study can be performed to test the metabolic and excretion rates of a compound in different animals. One reported study (Busch, Schmid et al., 1998) for an anti-inflammatory drug showed that rats and dogs produced similar metabolic reactions to humans, but were very different to mice, mini-pigs and baboons. The mini-pigs, however, produced the compound excretion rate that was most similar to humans. These studies can be used to see which animal is most likely to be a suitable human model (in this case it was the rat). It is of course easy in a comparison of the laboratory with the 'natural' to pick on differences and ignore similarities. Animal models are required because, whilst they might not produce a wholly accurate depiction of human disease, they do at least go some way to allowing researchers to gain valuable pre-clinical data and to reduce trial volunteers' exposure to potential harm.

For the BloodPharma team the use of animal models still represents an area of uncertainty. Although it was hoped that animal trials may not be required it is now clear that they will be expected by the regulators:

> *"When we went to meet with the EMA at first, I said "we are going to have to talk to them about the animal models we are going to use" and Y said "there's no animal models, we can't do any". I said "they are not going to accept that". So the first thing they said was "and what animal models are you…" Because, what regulator in the right mind would say "OK, just go straight into humans, on you go"."* (CS/Reg)

The difficulty with the cultured blood product is that unlike a standard pharmaceutical product there are many uncertainties surrounding the applicability of animal models for biologics and stem cell products, mainly due to the additional complications of the immune response. In conversations with the BloodPharma team it appears to be possible that human blood can be introduced into rats and pigs once without harm, but subsequent infusions could cause major immune reactions. Outside advice was being sought on the possible animal studies which could be used, as this was outside the area of expertise for those working on the BloodPharma project. Some of the researchers had limited knowledge about animal blood, for example they knew that birds have RBCs that are enucleated, but detailed knowledge of animal haematopoietic systems appeared to be a skill that was missing from the team in the meetings which I attended. It was, I believe, a representative of the Wellcome Trust rather than a scientific team member that thought to question whether mouse RBCs are even the same size as human RBCs.

A potential solution would be the 'humanising' of animal models by performing a haematopoietic stem cell transplantation in-utero, a technique developed in China using goat models. It was discussed that the regulatory restrictions will make it impossible for the animal studies to be carried out in China, which left the option of having to ship animal models from China to the UK. There is an expectation that smaller animal models may become available, although the literature would indicate these are proving more difficult to develop (Lin, Jun et al., 2008). The use of animal models by the BloodPharma team, although expected, was not something that appeared to be discussed in any great detail by the team. As an observer it appeared that the later human trials had been given more consideration by the team than the potential animal trials had. Animal trials rarely featured in any interviews or team meetings, although it is possible that they formed part of scientific meetings which I was not allowed to attend.

The ReNeuron trial had undertaken studies in rat models before human trials of ReN001 commenced (Smith, Stroemer et al., 2012). One trial attempted to mimic the affect of the loss of control over small motor movement often experienced by stroke

patients. The solution proposed was to use sticky tape applied to the paws of the rats, which were then monitored to see firstly how long the rats took to notice the presence of the tape and then how long it subsequently took the rats to remove the tape. A huge amount of regulatory discussion went into the development of the animal trials, and it was felt by the ReNeuron medical team that the authorities had primarily concentrated on the data obtained from these animal studies.

> *"There was a lot of different opinions about what the appropriate test to do in a rat was, and how many rats you had to look at. How many rat experiments you needed to do, and that was the focus of it."* (M/O)

The clinicians involved raised concerns that the focus of these early animal studies had led to discussions about the clinical aspects of future trials in patients being sidelined, as will be discussed below.

After animal trials, safety studies of the drug will move into three pre-marketing phases in human subjects, marking a gradual move from the totally controlled situation of the animal studies to the very open space of the final Phase III studies in a clinical setting. Here we see that the focus is still on the ability of the researchers to distil 'nature' into a controlled environment, tempered with the controls introduced to minimise harm to human trial participants. The first phases include small doses and look only for safety, only later is it permitted for the dose to be increased and for efficacy to be studied.

Perhaps the key factor of human clinical trials is 'extrapolation', the ability of a small cohort of subjects to be indicative of the results that should be seen were the product to be administered to the population as a whole (Rothwell, 1995). In reality early trials are often carried out on young, healthy, non-smoking male volunteers. Only later are patient groups trialled who may, in addition to having the disease being studied, be overweight, of different gender or ethnicity, taking a variety of medications, and forgetful regarding correct dosage or timing. For example the early Phases of the ReNeuron trial did not allow the drug to be administered to women. This is because the cell culture method includes the use of Tamoxifen, giving a theoretical risk that subsequent treatment for breast cancer in a volunteer may

increase the tumorigenesis risk if cells were kick-started to turn from neural cells back into pluripotent cells.

For the BloodPharma team the key goal at the end of the Wellcome Trust funding is to have obtained a method for producing cultured RBCs at the quantity required for a first-in-human trial. The researchers were all very clear that for the first studies this quantity would amount to millilitres of product rather than anything on a larger scale. In keeping with earlier references to past clinical trials where adverse events have occurred my data shows that there is a strong emphasis on safety and on conducting any human trials to the highest possible regulatory standards. One interviewee commented that "people are not guinea pigs".

Very early trials looking for safety can only be carried out in healthy volunteers, with the advantage that such people are readily available in close proximity to the research centres taking part in the BloodPharma project. In keeping with the uncertainties of the potential animal models the human trials also raise questions of immune rejection which are not present in pharmaceutical trials. Although the team are seeking to make O negative, universal donor, blood it is unlikely that they will achieve this before the first study. Their option is simply to recruit volunteers who match the blood type of the cultured RBCs, for example an A negative blood type. This however introduces the possibility of the team having to go through Phase I, and possibly Phase II trials, more than once (as it is unlikely that the two different forms of blood will be considered the same 'product' by the regulators).

Whilst this is physically possible it is difficult to envisage how the project will manage this sort of iterative process without being financially crippled. Further studies which move towards demonstrating efficacy will necessitate the use of cultured blood in patient populations. These potential target populations are explained in more detail in the next section, but it is likely that thalassemia patients will form one of the initial clinical trial groups. Thalassemia was considered to have a slight advantage over sickle cell anaemia in that sufficient patients might be found in Europe. In keeping with the wishes of the team to obtain the highest regulatory

approval possible it is considered that approval from the European regulators is the only route down which to proceed, as one interviewee commented:

> *"And the clinical trials on western soil. Because whether we like it or not the standards are much higher and the oversight is much more exact."* (CS/Med)

The first challenge for the ReNeuron stroke trial in humans was patient recruitment. Whilst hundreds of willing volunteers came forward the strict criteria imposed meant that few were eligible to take part. Patients were required to be male, above the age of 60 and live reasonably close to the hospital, to have suffered a particular type of stroke and to be at a stable stage in their stroke recovery, where it was to be reasonably expected that they would not improve independently. Another critical area in the clinical trials design was the decision about whether or not to use immunosuppression. The brain is often considered to be immunologically privileged, therefore not requiring immunosuppressant use, and there have also been previous studies injecting tissue into the brain which have not shown inflammatory reactions.

> *"And the animal experiment people, certainly the attitude from some of them involved in the review process, was 'oh but it wouldn't be too difficult just to give them* [the patient volunteers] *cyclosporine for 6 months'. To which my response was 'it certainly would. It's a highly toxic drug, immunosuppression is a dangerous thing to do to patients, it's got numerous drug interactions in people that are taking lots and lots of drugs already, and I do not want to do this to a patient'. It's very dangerous."* (M/O)

These examples from the ReNeuron trials demonstrate just some of the challenges associated with running a clinical trial in humans. Firstly there is the difficulty of recruiting suitable patients and ensuring that the clinical trial requirements are not too onerous for them to undertake. Then there is the additional decision about whether the use of immunosuppression is required for the particular cell line and part of the body that is being studied. The ReNeuron trial has entered the regulatory system a few years before the BloodPharma trial will, yet there are similar lessons to be learnt about the challenges of balancing the views of scientists, clinicians and regulators, especially once human volunteers enter the equation. There are also practical considerations to be considered when undertaking a clinical trial. For example at one team meeting the problem of production for a clinical trial was

raised. Blood does not keep for long periods, so in the case of the BloodPharma project how will this effect recruitment and trials? If each cohort is given a freshly produced batch of blood then there is an expectation that the regulators may consider that the product being tested is not the 'same' for each patient. Conversely if you wish to give each patient blood from the same batch then it may mean injecting all the patients over the period of a few days, precisely the situation that clinical trial designs try to avoid in case adverse reactions occur. This storage situation is one that could be argued is unique to the BloodPharma team. Other stem cell therapies may also have the potential challenge of batch production but RBCs are the only cells in the human body not to contain a nucleus. The BloodPharma team therefore face a distinctive time constraint, a deadline of 120 days before the cells die completely

The clinical trial methodology outlined above has grown out of the regulations put in place for pharmaceutical products, but it has been seen that stem cells pose unusual challenges in storage and potential immune rejection. There are additional challenges which are exclusive to stem cells and which have been identified by interviewees and the wider stem cell field. The primary challenge for clinical trials of stem cell therapies is the issue of engraftment. Many stem cell therapies involve the injection of living tissue which has the ability to replicate in the body, indeed the replacement of damaged tissue in this way is the aim of many cell therapies. This however brings additional problems in that the cells will be alive and multiplying in the patient, potentially for many years to come, and have the possibility of forming teratomas. This problem should not apply to the cultured blood product which will, if produced correctly, have no danger of multiplying in the body. In conversations with the BloodPharma team they often mentioned that whilst drugs 'went in one end and out the other', other stem cell products would stay and multiply in the body. This is not to suggest that pharmaceutical products are not capable of causing adverse reactions, rather that these drugs would be metabolised over a relatively short period of time. This longevity of the cells has implications for stem cell trial volunteers, for example patients in the ReNeuron trial not only have to subject to the barrage of testing necessary during the trial but also consent for post-mortem brain examinations.

Ethical implications are therefore raised in the use of healthy volunteers, as it is considered that injecting healthy patients with stem cells into areas such as the heart, spinal cord or brain, would be putting them at a risk which outweighed the benefits obtained from the clinical trial data. Stem cell trials are also difficult to placebo, as this would involve injecting into vulnerable tissue without any potential benefit. Even if this were shown to be ethically acceptable it is very hard to blind the study as the bags of tissue used would have to look identical both to the patients and to the doctors. To this end both the ReNeuron stroke trial and the (now discontinued) Geron spinal cord trial used patients (rather than healthy volunteers) for first-in-human studies and did not use placebos. The balance between using 'unhealthy' patients and wishing to identify potential teratoma risk came to the fore during the planning of the ReNeuron trial. In an effort to protect patients the regulators insisted on a higher age limit of 60 years, as opposed to the 40 year limit proposed by the researchers. This caused some concern to the medic that I interviewed:

> *"Age limit was the specific thing that they insisted was changed, upwards. Which from a clinical perspective is a problem. My concern is that older people don't tolerate anaesthesia and invasive procedures as well as younger people. And when you are dealing with people over the age of 60 with stroke, as supposed to over the age of 40 which was the original proposal, you are compromising patient safety in other respects, potentially."* (M/O)

In combining safety with ethical considerations the trial ended up using a cohort of patients who were both elderly and in many cases had numerous health problems in addition to the effects of the stroke. The interviewee was concerned that in the regulatory review of the safety aspects the views of the clinicians who worked on a daily basis with such patients were not taken into account, and that this had resulted in patients being put under undue pressure:

> *"And we have seen what I anticipated, which is that at least one of our patients so far said that he couldn't go through another scan, won't go through another scan because he can't tolerate it. It's very uncomfortable for him, he has to lie there for a long time. Can't communicate easily so he can't let people know if he is uncomfortable, if he needs to go to the bathroom etc."* (M/O)

Although there are lessons to be taken from the balance of risk versus patient health it will be interesting to see how the regulators react to the BloodPharma trial, given

that the cells should not engraft or form teratomas as they have no nucleus. This is just one of the uncertainties facing the BloodPharma team as they attempt to move their product through the regulatory system. The contrasting ReNeuron trial has demonstrated that even further down the regulatory pathway there are still debates about the correct clinical trial procedures to ensure both the safety of the trial participants and future patients.

THE IDENTIFICATION OF SUITABLE TARGET POPULATIONS FOR THE INTRODUCTION OF THE CULTURED BLOOD PRODUCT

Given the huge scale-up challenges for the BloodPharma product, and the likely high cost of the initial product, there are plans to introduce cultured RBCs using a stepping-stone method. This would see the product being gradually introduced to key target populations, building towards a wider introduction to more general medical usage. The aim throughout the BloodPharma project has been to make the cultured blood indistinguishable from donor blood, and the team has ensured that the technology can be implemented in an incremental way. The storage and distribution infrastructure are already in place for the BloodPharma product, as it is currently expected that the cultured blood will use the same (or similar) bags, needles, staff, transfusion method, storage, as the current donation system. This allows the cultured blood product to be introduced using a gradual process, with the use of target populations allowing the product to be first produced and used at a much smaller scale, without the challenges of supplying the entire blood transfusion system.

It has been difficult to obtain a definitive answer from the BloodPharma team as to the cost of the eventual cultured blood product. There is an agreement that long-term the cost of the cultured blood product must be in line with the current costs of donated blood (either £800 if the total cost of infrastructure is used or £140 if the price is based on what a hospital pays for one unit of blood). This would however be the cost of production at a large scale, for smaller numbers it is likely that the cost would be significantly above £800. The use of target populations could make this increased cost acceptable by changing the view of the cultured RBCs from a transfusion to a sophisticated pharmaceutical. Some of the proposed target

populations are discussed below, but a common factor in all of these populations is that the use of cultured blood is expected to produce benefits above those of ordinary donated blood.

When asked whether the NHS would consider providing the cultured blood product one interviewee responded:

> *"The NHS does provide stem cells therapies. The NHS would provide stem cell therapies if they were effective and low cost, with regulatory approval and were shown to be cost effective over the piece. In other words, you would work out the cost of the procedure, the Quality Adjusted Life Years gained and offset by the cost of other treatments avoided."* (CS/Med)

Whether such treatments can be funded by a public health service often hinges on the relative cost of treatment, as the aim of any health care provider is to achieve maximum patient benefit for the available budget. Assessing the cost effectiveness of a drug or treatment regime, however, is a complex process. The Quality Adjusted Life Years (QALYs) referred to by the interviewee are an important consideration in assessing the affordability of a new medicine or therapy. QALYs are used to measure the cost effectiveness of different medical treatments and are a measure of both lifespan and health. One year of full health is assigned a value of 1.0, with death being 0.0. Ill-health is the range in between, for example a year of ill-health may score 0.6 (Bravo Vergel and Sculpher, 2008). QALYS can assist in analysing the benefits versus costs of different treatment regimes and QALYS are often used in analysis of health care economics due to their simplicity and ability to represent complex healthcare choices as a quantitative value. This is also the criticism of QALYS, that they rely on clinical decision making and do not allow for patient autonomy (La Puma and Lawlor, 1990), and that they focus on population care at the expense of individual patients (Loomes and McKenzie, 1989). Despite the criticisms of the QUALY measurement it is used as one of the main determiners of the cost effectiveness of treatment in many countries, including the UK (Eichler, Kong et al., 2004). As a guideline the National Institute for Health and Clinical Excellence (NICE) considers treatments of less than £20,000 per QUALY gained to be cost

effective, with treatments over £30,000 per QUALY gained requiring additional consideration (NICE, 2007).

Donated blood is currently an effective therapy for the vast majority of the population, however there are minority groups for which the cultured blood product could provide a significant improvement.

> *"So there would be situations where we don't have blood donation as a source, and that would obviously be the first routes for use. Maybe medical conditions that couldn't take blood from somebody else, you would have to be more sure of the source, immunosuppressed people, you know that the cells that they would be given would have to be pure and free of anything else."* (CS/Lab)

Cost effectiveness may become more apparent when taking into account the money currently spent on long-term care of such patients, including the treatment for side-effects of the current treatment regimes.

One target population identified is sufferers of sickle cell disease, which results in distortion of the RBCs[4]. The trait is most commonly found in people from Africa, Asia and the Caribbean, with some prevalence in Middle-Eastern and Mediterranean populations (Anie, Steptoe et al., 2002). Sickle cell is a devastating disease in Africa, where the constant medical attention required by sufferers is not available, as we previously saw from the interviewee who had worked in this area.

> "*So anyway, we go there and wandering around Northern Ghana, where sickle cell disease is endemic.. so one in four of the children die, children of a couple of carriers, and 2 in 4 are cariers and 1 in 4 gets malaria, sadly. So it's an awful gene.*" (CS/Med)

Currently sickle cell sufferers are transfused with blood to help them overcome various types of 'crises', such as sickled cells blocking capillaries. As they are often multiply transfused throughout their lifetime they can develop severe immune reactions to blood that is even slightly mis-matched. Finding donors that are an

[4] It is a co-dominant gene, so an individual who was heterozygous (have one healthy gene and one sickle cell gene) for the sickle cells trait would make half normal RBCs and half sickle cells. In individuals who are homozygous for the gene (have two copies of the sickle cell gene) the disease is generally fatal without medical intervention. The sickle cell trait confers some protection against malaria and this gives an advantage to heterozygous individuals, who are protected from both the full-blown sickle cells disease and malaria.

appropriate match is more difficult due to the lack of donors from ethnic minorities in the UK. Cultured RBCs could allow improved matching of blood to patients and for that same blood to be given every time, preventing immune reactions due to patients receiving blood from a variety of donors.

Thalassemia is another blood disorder identified as a potential target population for RBCs as a therapeutic. Again it is an inherited disorder which results in the production of abnormal haemoglobin and is treated using multiple transfusions. Thalassemia patients who are regularly transfused suffer problems with iron loading, for which drugs must be administered (Clemente, Congia et al., 1994). These drugs also produce unpleasant side effects and the use of multiple transfusions ultimately results in a reduced lifespan. In current transfusion cells will be a mixture of ages, with some nearing the end of their life, meaning a proportion of the transfusion will be destroyed by the recipient's body.

> *"I mean, one of the unique selling points is that the cells from culture are all fresh, they are all day 1. When you take an armful from a donor a proportion of it is already coming near the end of its life. So after 20 days storage, which is oldish, about 20% of it is immediately mopped up in the spleen and destroyed. Whereas one would anticipate if they were all fresh then that would be a very small percentage of stuff that would be damaged." (CS/Lab)*

Cultured blood transfusions are expected to be required less frequently (as all the cells produced will be 'new'), reducing side effects for patients and extending their lifespan. Currently it is expected that the first target population for cultured RBCs use will be thalassemia patients. This is due to the requirement for patients to be used in clinical trials which satisfy the UK and European regulators. As thalassemia patients are found in populations of Mediterranean origin this gives the potential to recruit enough patients to conduct a clinical study in a country which is still under the remit of the European regulators.

As we saw in the previous section, supplying the entire blood transfusion service may be a challenge which takes up to 20 years to overcome. The use of target populations may help to realise the team's ambition of getting cultured blood into clinical use within a shorter time frame. The use of cultured blood for these

populations may also allow the product to be produced at a higher cost, whilst still keeping within approved cost effectiveness ratios. This is due to cultured blood providing a therapy which goes above and beyond the efficacy of donated blood, as one interviewee explains:

> *"Yes, so it [cultured blood] would have to be cheaper [than donated blood]. Or so much improved that it was indefensible not to spend the extra money.* (CS/Lab)

Despite the expected benefits to patients the use of target populations does provide some challenges in the form of clinical testing and tissue matching. The team wish to carry out testing with Europe in order for the clinical trials to fall under the jurisdiction of the European regulators, however finding a suitable number of patients may be challenging. As we saw with the ReNeuron trial there are very strict criteria for eligible patients, which could prove problematic if a target group (e.g. thalassemia patients) were required for Phase 2/3 trials, which normally use a large number of volunteers. One interviewee felt that the US may be a better route to regulation and licensing of the product, because of the combination of increased patient numbers and the very good orphan drug program, which could allow a quicker route through the regulatory system.

> *"The FDA have a better orphan drug program than the MHRA, so where we are talking about these guys with sickle cell disease, they have a lot of people on American soil, a lot of Americans, who have sickle cell disease who need transfusion and who they can't keep up with. Much bigger African genetic population than we do, anywhere in Europe. So their need is greater, but they also have this fairly good orphan drug program"* (CS/Med)

Although the US may represent a route to market Europe is still being treated by the BloodPharma team as the initial area of licensing.

Whilst much focus is often given to target populations with specific blood disorders there are also other minority populations within the wider blood transfusion model. Although these patients are unlikely to benefit from cultured blood over donated blood, they do currently receive blood which is more costly than the standard, making them ideal candidates for being the next 'stepping-stone' to introduction. Currently the blood transfusion services in the UK have to operate around the clock

because unexpected trauma patients may require more blood than is held in stock by the hospital. Blood is processed at a central site and then taken to the hospital, sometimes by taxi, courier or the Nationwide Association of Blood Bikes (volunteers who provide motorbike courier services for the NHS). Emergency blood is therefore comparatively expensive due to the cost of distribution and the extra wage costs associated with staff working unsociable hours. If cultured blood could be used to obtain large quantities of O-negative blood there would be no need for matched blood to be distributed to trauma patients and the blood transfusion service could potentially operate on a 9-5 basis, greatly reducing overheads.

This section has presented some of the suggested target markets for the introduction of the BloodPharma product. These uses are based on using the existing infrastructure of the current donation system, but would replace conventional blood donation with a product that is likely to have increased benefits for certain patients, and reduced infection risk for the wider transfusion field. In the next section further changes to the product itself will be discussed.

HOW DOES THE BLOODPHARMA TEAM IMAGINE FUTURES BEYOND THE FIRST PRODUCT?

Currently the focus of the BloodPharma team is primarily on the short term goal of providing enough cultured RBCs to be used in a clinical trial. The long term goal of supplying the UK transfusion service may be 20 years away and there is the potential for technological improvements to the product during that time. Some of these improvements may not yet be known but others are anticipated and discussed by the BloodPharma team, even though the technology to implement them has not yet been fully developed. Forward thinking is a practice common to all science and innovation and it plays a vital role in bringing together the expertise and resources required to see a future vision through to completion (Borup et al., 2006).

The team discuss prospective changes to the product because these future visions are necessary for it to make decisions in the present regarding appropriate developmental pathways. Expectations for therapies are often focused on the period of translation

from laboratory to clinic and are crucial for facilitating this move from bench to bedside. Martin et al. (2008) refer to 'communities of promise' in order to highlight the importance of translational networks sharing a common goal, or vision, of a future technology. Wainwright et al. (2006) also consider the bringing together of scientists and clinicians as playing a vital role in assisting this translation, something which the BloodPharma team has done from the start. In building these anticipated futures the team have also been insistent that it refrains from promoting the 'hype' which stem cell science has been associated with in the past.

> *"They're [the Wellcome Trust] not expecting us to be injecting people in three years time. It's all the external hoo-ha that's engendering that."* (CS/Lab)

Stem cells have previously been associated with expectations and promises which have not been borne out by actual therapy developments. Some of this hype has been associated with areas such as embryonic cord blood banking (Brown and Kraft, 2006), where parents have been enticed to pay fees in the hope of safeguarding their child's future health.

The blood type used for the clinical trial is not of great importance, provided suitable volunteers could be found, as this quote demonstrates:

> *"That [universal donor] would be preferable, you need an O negative human stem cell line for that, but I think that would be the end goal of the work over ten years or so, that's not necessary to get to our endpoint for this grant. If the cell line happens to be A pos for example we would just transfuse it into an A pos individual."* (CS/Med)

It is clear then that the BloodPharma team has a series of long term goals which it is aware may take many years to achieve. It also appears to view clinical trials as an iterative process and is willing to go through the first stages of clinical trials a couple of times, perhaps first with an A positive (for example) and then later on with the universal donor that it is aiming for. From talking to the team it would appear that the primary long-term goal is the eventual use of iPS cells. Induced Pluripotent Stem Cells (iPSCs) are cells of somatic origin which have been 'reprogrammed' to an embryonic-like state, and are therefore pluripotent and capable of forming many different tissues. The first iPSCs reported to be created from human cells were made

in the Japanese lab run by Shinya Yamanaka in 2007 (Takahashi, Tanabe et al., 2007). Originally viral vectors were used to introduce small amounts of DNA into the somatic cells, but more recently the move has been towards using chemical compounds to stimulate the DNA of the cells. The potential use of iPS cells at some time in the future of the BloodPharma project has always been discussed by the team, however the reasons for choosing iPS technology has changed over the past few years. During initial discussions with the BloodPharma team it was proposed that iPSCs cells could be used the answer to finding the elusive 'universal donor' cell line. The O negative blood type is found in about 7% of the population, so embryos with this blood type are rare.

> *"And also just from pure practicality that making embryonic stem cells we don't currently screen the embryos so we don't know what genotype they're going to have, we don't know what blood group they are." (CS/Lab)*

It appeared to be apparent to the team that finding a suitable blood type from embryonic stem cells lines would be unlikely. At the times of the earlier interviews there were some reservations from researchers about the use of iPSCs, which, despite the rapid progress of the technology, had only been around for a few years.

> *"I do think there's a role for iPS, if that's the technology that becomes the best. Having said that there appears to be some drawbacks with the current iPS lines in these protocols, but I think an alternative pluripotent source will arise, and again the technology is advancing so phenomenally rapidly, like nothing else has advanced. That in five years time it will be done and dusted and the cell source will be there. And I think a lot of the protocols will be applicable to other pluripotent cells as well. So, we're doing the groundwork that can be reapplied as and when, probably the Japanese, sort out the cells for us."* (CS/Lab)

Although at this point it was not clear whether iPS cells would be the answer, it was certain that what was required was some sort of pluripotent cell line which did not involve the use of embryonic tissue. It did appear to be that the primary goal for creating this pluripotent line from a somatic cell (such as a skin cell) was the increased chances of obtaining an appropriate donor, both for the universal donor line and also for the minority populations such as the sickle cell and thalassemia sufferers. This would have to be achieved by obtaining tissue from a consenting donor who provides the best possible match for a target patient group. Although

biologically useful there would of course be ethical implications of doing this, and my data shows that the team were aware that iPSCs at the time were not as well defined or tested as embryonic stem cells.

> *"And again I think the iPS bandwagon is being jumped on a lot in the states because it's ethically more acceptable than embryonic, but it has its own risks as well*." (CS/Lab)

IPS cells are also often heralded as an 'ethical' alternative to using embryonic stem cells as they do not involve the destruction of an embryo (Kastenberg and Odorico, 2008). This argument fails to account for the very real ethical dilemma that these cells would most likely be taken from a living donor. Whilst consent processes have moved on from the time of the HeLa cells[5] there are still questions to be asked about the appropriate consent that could be taken when a (potentially multi-million pound) therapy is made from the cells of a donor who is still alive. As many of the target diseases identified by the BloodPharma team predominantly affect people of ethnicities which are in the minority in the UK it is possible that the 'best match' for these disease populations will come from another country. There is also the option to create autologous therapies, by taking cells from an individual patient and growing blood that is an exact match to them. This would obviously be very expensive and could only be used in extreme cases.

During the period I followed the project (2009-2012) the emphasis for iPS cells changed from being a potential method of obtaining a matching donor to a means of securing much needed intellectual property rights over the cells and methods which the team are developing. This change was due to a patent ruling which became known as the Brüstle decision. In 1997 Oliver Brüstle, a German neuroscientist, was granted a patent on the process of developing human neural precursor cells from embryos, the neural cells being required for his work on Parkinson's disease. In 2011 Greenpeace challenged the Patent decision, claiming that it went against EU Biotechnology Directive which did not allow the *'use of human embryos for*

[5] The HeLa cell line is the most widely used cell line for stem cell research. The line was created in 1951 from the cells of a poor black woman who had no knowledge that her tissue was being taken for research. The story of this process was brought to wide public attention in 2010 in a best-selling book, 'The Immortal Life of Henrietta Lacks', by Rebecca Skloot.

industrial or commercial purposes' to be patented in any of the EU member states (Herbert-Smith, 2011). The main questions raised by the case were whether research activities were considered to be industrial or commercial purposes, and whether the non-patent rule applied only to the cells themselves or to the method. On 18th October 2011 the European Court of Justice decided that the EU Biotechnology Directive did prevent the granting of patents which involved the destruction of an embryo, regardless of the stage at which this destruction had occurred and even if the patent was for the process and did not itself refer to the embryonic stem cells (Plomer, 2012).

The ruling caused widespread shock amongst the research community, which considered the ruling would have a devastating impact on investment in cell therapy research (Holmes, 2011), although there is some feeling that the impacts may be lessened by the ability to patent outside Europe or to take advantage of orphan drug funding (Davies, 2010). Since this ruling there appears to have been a shift in the goals of the BloodPharma team, from using iPSCs solely as a source of rare blood types sometime in the future, to an urgent need. Techniques developed using iPSCs are allowed to be patented, and once the techniques are patented these patents will also offer protection to production using embryonic stem cells. The focus now appears to be on moving forward the iPS cell research so that the financial investment made in the project can be protected. The implication for the team is that they will be required to develop an entirely different technology strand whilst simultaneously continuing to work on the embryonic methods which they have already invested in developing. It still appears to be uncertain whether the embryonic or the iPS cell technology will be taken through to clinical trial, although it is likely that the already advanced stage of the embryonic work will mean it is used for the first trials.

Although this project is taking place in the UK there is awareness amongst the researchers that the UK is lucky in already having an established blood donation system. Although infections do occur they are extremely rare and there is a low level of endemic disease in the general population. There is even greater potential for the

use of this technology in other countries, including places like India, with increasingly sophisticated medical technologies but high levels of endemic disease. The goal when talking to the BloodPharma team does seem to be Africa, which has the highest number of deaths per year due to post-partum haemorrhage (Drife, 1997). There are long-term plans to make the cultured RBCs storable at room temperature, which will not only allow for ease of storage in the UK but will additionally allow the blood to be transported more easily. There have been differences of opinion within the team over whether the blood will ever be storable at room temperature, or indeed if this is any benefit for warmer climates.

> *"I thought that was the ultimate aim, so universal donor blood and room storage. Now for Africa room storage doesn't really help, because 40 degrees isn't our room storage. So, it may need to be refrigerated. …And the stability study that you would set up for those countries and those humidities, because it's a plastic bag which humidity could have quite an influence on, so that type of thing."* (CS/Reg)

So we can see here that although countries such as those in Africa appear to be an eventual target there is a change in infrastructure required before cultured RBCs can be widely used. As the researcher above has pointed out, even advances in storage temperatures may not be enough to cope with the high heat and humidity, resulting in the requirement for additional refrigeration. There is also the consideration that without medical care an adequate supply of blood would be useless, and many women dying of post-partum haemorrhage in these countries are many miles away from the nearest hospital. Whilst cultured blood could provide a clean blood supply in countries with a high prevalence of potentially transmissible infection, the use of this blood depends largely on the storage and delivery infrastructures available.

CONCLUSION

This chapter has addressed the key challenges identified by the BloodPharma team in translating cultured blood into viable clinical practice, and how these challenges shape everyday practices. Building on Chapter Three, which focused on basic research in the laboratory, we have now seen the team move out of the laboratory space to consider the implications of scale-up and clinical trials.

The scale-up requirements of the BloodPharma product are unique, demanding volumes of cells which are unprecedented in the stem cell field, and we have seen how the technology commonly used in other fields may not be applicable to a product which contains delicate cells. The methods of growing and sorting these cells are still unclear, but it appears certain that a new industry will have to be created to cope with the high demand for blood in the UK and worldwide. The scale-up of the BloodPharma product causes questions concerning the implications for automation and standardisation within the stem cell field as a whole, particularly linking with the problems of tacit knowledge as discussed in Chapter Three. In an industry that requires consistency as well as quality the reliance on visual identification and hands on experimentation becomes a challenge requiring the development of increasingly sophisticated automation technologies. In the case of the BloodPharma project we have seen how the team must look forward many years into the future, attempting to introduce scaleable protocols and to develop the large bioreactors required even when a small quantity of product cannot yet be produced in the laboratory. This is a clear demonstration of the challenge ahead of the team, and that they are aware of the many years it will take to develop the systems required for translation.

The ultimate goal in producing large quantities of blood is to eventually supply the UK transfusion service; however the first hurdle is to produce enough product to be used in clinical trials. We have seen that the model for animal and human trials within the stem cell arena is still contested and uncertain, and the BloodPharma product is no exception to this. The applicability of animal models and the ethical acceptability of using human trial volunteers has been questioned by the larger stem cell community, yet the requirement for some form of safety testing is clearly acknowledged. Again we see the BloodPharma product as occupying a niche within the stem cell field, given that the product does not have the same DNA transfer potential, or the same longevity, as other stem cell therapies. Here the ReNeuron trial has been drawn upon as an example of a more ‘standard’ stem cell therapy which is also further down the clinical trial pathway. The requirement to develop new animal models has been shown, as has the clash between the regulators and the clinicians over the appropriate patient cohort and clinical trial design. The clinical trial process

for the BloodPharma product is still unclear, but it is likely that the product will introduce some new considerations for the regulatory bodies.

Given the huge scale-up challenge the use of a stepping stone method of introducing the BloodPharma product was discussed. The identification of potential target groups, such as sufferers of sickle cell disease or thalassemia, could allow the product to be used in smaller quantities for selected patients. These patients are likely to benefit from cultured RBCs over and above the general population, and would allow the BloodPharma product to be introduced with lower volume requirements and in a way that would justify the high initial cost. After introduction of the product using these target groups there is potential for the product to be rolled out by concentrating on other high-expense groups, such as emergency patients, as it is likely that money could be saved by the blood transfusion services by reducing the pressure on out-of-hours staff and services. Potential changes to the cultured blood product have also been discussed by the team, most prominently the use of iPS cell technology. Whilst this is a way of obtaining an accurate donor match for target populations, or a universal donor for wider transfusions, more recently the advantage for patenting has made this an increasingly attractive option. Whilst the impact of the Brüstle patent decision to the long-term future of the stem cell field is not clear it would be advantageous for the BloodPharma team to secure as many rights as possible over its work and the product produced. Other long term aims, such as making the product storable at room temperatures, may contribute to storage and distribution within the UK, although supplying areas such as Africa is likely to rely on other advances in storage and administration infrastructure.

The key challenges associated with translating cultured blood into a viable clinical product are therefore seen to be associated with scale-up and standardisation, the uncertainty of the clinical trial regime and the initial introduction mechanism for the cultured blood product. Such challenges are shaping everyday practices as the team seeks to work towards these goals many years ahead of implementation. For example members may be attending a meeting about the development of a bioreactor when the cells themselves can only be grown in small quantities. Protocols for cell culture

are already being designed for scalability, even if this means increased work at the present time, because the team are aware that they must develop standardised protocols which are future-proof. Similarly potential animal models are being considered and target markets identified whilst the early stage laboratory work is continuing. In considering such target markets the team are researching the most likely blood types to be required, the potential location of trials and the funders who may be interested in such work. Whilst the impact of the regulatory system on the translation of this product from basic laboratory research to clinical therapy has been touched upon in the context of clinical trial design, the next chapter will deal in more depth with the BloodPharma team navigating this regulatory pathway.

CHAPTER 5: REGULATION IN THE BLOODPHARMA PROJECT

INTRODUCTION

Stem cells are complex and volatile products capable of producing both benefit and harm to patients and therefore requiring appropriate regulatory control, in the form of a regulatory system which both mitigates risk and supports the development of new therapies. As Harmon et al. (2013, pg.26) write "*We expect our governance frameworks to defend against risk and to promote a range of valued outcomes, including better health, safety, productivity and prosperit*y". The UK system for regulating stem cell based products is complex, and seeks to reflect the unique properties of stem cells and the safety considerations which these bring. The ethical and moral implications of stem cell research have received much attention both in the lay press and in academic discussion, in comparison to which the applicability of the current stem cell regulatory system has been overlooked (von Tigerstrom, 2008). In this chapter I will focus on the dynamic and evolving relationship between the BloodPharma project team and the regulatory system, to explore how the regulatory system works in practice during the development of a novel stem cell therapy.

The overarching research question is:

How does the regulatory system, and perceptions of risk, shape the activities of the BloodPharma team and the development of the cultured blood product, and what can this case study tell us more generally about the regulatory system for stem cell products?

In the first section I will present an overview of the current regulatory system and identify the key regulatory bodies that impact on the BloodPharma team. Drawing on the literature around regulatory theory I will consider how the regulations for stem cells in the UK have been built up over time and what each of the regulations was designed to protect. Moving from early tissue use through to market authorisation I will draw on interview and observational data to explore how the regulations for each

stage are working in practice, and where there are important boundary issues between the different regulatory bodies.

The second section will consider how the BloodPharma team is navigating the regulatory system. Drawing on different notions of expertise I will consider the various levels of knowledge, information and capabilities required. The laboratory researchers have a specific kind of scientific expertise and knowledge but find themselves less able to engage with the language of formal regulation. Translation is therefore required between the scientists and the regulators to turn the basic scientific data into suitable regulatory dossiers for presentation to the regulatory committees. The BloodPharma team is able to draw on many members of staff with differing expertise, but this is not always the case for other projects and may be a barrier for many academic researchers.

In the final section I will explore the product itself in the context of regulation and consider how it may be perceived by the regulators and how future hurdles are being anticipated by the project team. The team, I will argue, use 'informal reasoning' to make sense of the potential risks associated with their product, and I discuss this using Sadler and Zeidler's (2005) work on informal reasoning considerations. As the BloodPharma team is developing stem cell lines which they hope to use long term, they face uncertainty about future regulatory requirements. To avoid falling short of safety levels which are subsequently introduced, the team have to look ahead to anticipate future regulatory hurdles and plan the scientific work accordingly. Here the BloodPharma team has the challenge of balancing the introduction of a novel product with the use of an already established technology.

The BloodPharma project can be considered a test case for the regulatory system due to the unique combination of a starting embryonic stem cell line with the eventual enucleation of the end product. This enucleation should result in no DNA transfer to the recipient, giving the BloodPharma product a different risk profile from many other stem cell derived therapies. There is currently much uncertainty about both the scientific work and the way in which the project will navigate the regulatory system.

The regulators are also learning and seeking to develop appropriate methods of regulating a fast moving field. This chapter will provide a snapshot in time of a team attempting to engage with the regulatory system and consider what these uncertainties can tell us about the regulatory system itself and the appropriate oversight of stem cell therapies more widely.

IDENTIFYING THE EMERGENCE OF THE KEY REGULATORY BODIES AND OUTLINING THE CURRENT REGULATORY SYSTEM FOR STEM CELL RESEARCH IN THE UK

This section analyses the emergence of stem cell regulations in the UK and the impact of this on the characteristics of the current regulatory system. Firstly relevant regulatory bodies will be introduced, alongside relevant regulatory theory, and secondary data used to consider how the main stem cell regulations in the UK were created. I shall then use examples from my own data to illustrate boundary issues which have arisen as the BloodPharma team, and other scientific projects, has attempted to navigate this system. The regulatory system for stem cell products in the UK is currently comprised of a significant number of different regulatory bodies, which are responsible for overseeing both safety and ethical aspects of the stem cell field. This complex regulatory route is outlined in the Interim Regulatory Route Map, Figure 12 (included in Appendix). Before discussing this regulatory system in more detail I will present a brief overview of some of the main regulatory bodies and their remits. This list is by no means exhaustive as there are many other agencies that regulate other parts of the stem cell field and laboratory work in general[6]. It serves to illustrate the complexity and potential for overlaps.

Human Fertilisation and Embryology Authority (HFEA) - oversees the Human Fertilisation and Embryology Act, which sets out the requirements for the collection, storage and use of embryos and gametes in the UK. **(www.hfea.gov.uk)**

[6] These include the Department of Health, the Home Office (for animal work), the NHS Blood and Transplant Authority, the Advisory Committee on the Safety of Blood, Tissue and Organs, etc.

Human Tissue Authority (HTA) - Responsible for regulating the use of human tissue in the UK, including tissue transplants, tissue banks, laboratory samples, and the collection and use of adult or foetal tissue in research. **(www.hta.gov.uk)**

Medicines and Healthcare Products Regulatory Agency (MHRA) - Regulates medicines, devices, Advanced Therapy Medicinal Products[7] (ATMPs), and blood within the UK, including safety testing, licensing, and reporting of adverse events. **(www.mhra.gov.uk)**

Gene Therapy Advisory Committee (GTAC) - The committee with ethical oversight of clinical trials involving stem cells or gene therapy. GTAC was disbanded in June 2011, with responsibility passing to the National Ethics Committee[8].

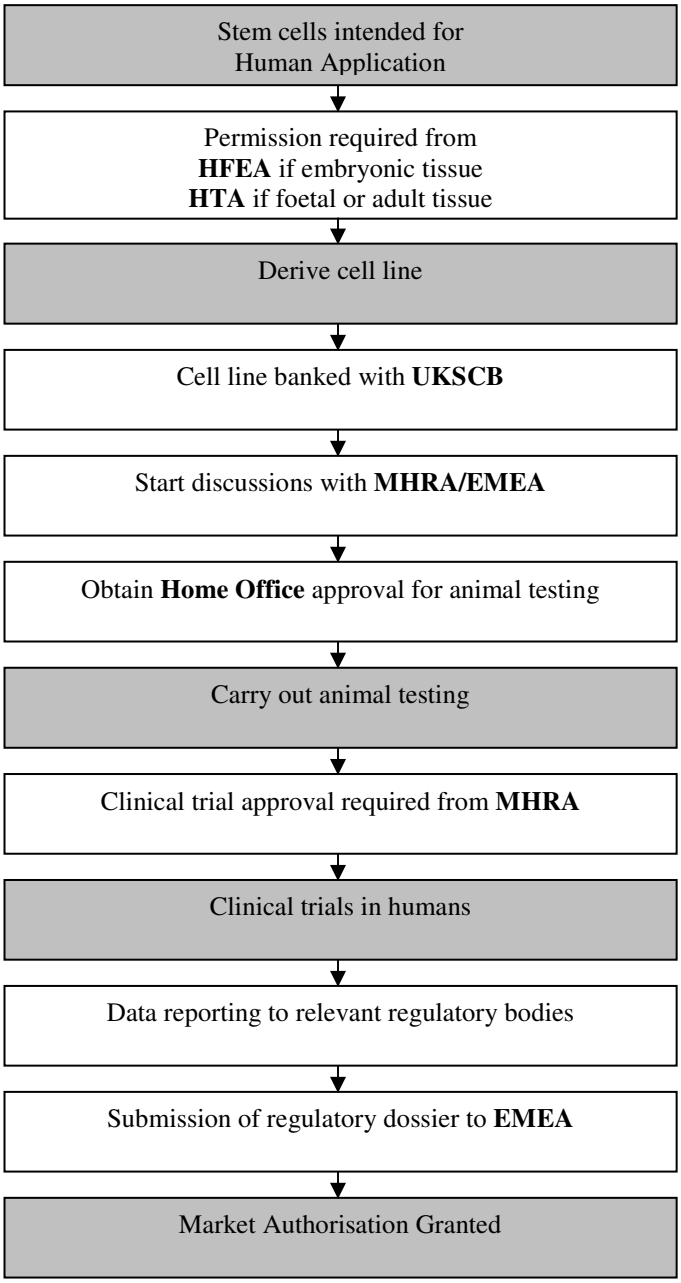
UK Stem Cell Bank (UKSCB) - May not strictly be considered a regulatory body but oversees the transfer of stem cells between research teams, banks research lines and works on maintaining stable derivations of such lines. **(www.ukstemcellbank.org.uk)**

European Medicines Agency (EMA) - Provides a centralisation of the scientific evaluation required for the marketing authority of medicines across the European Union (**www.ema.europa.eu**)

[7] The HTA defines ATMPs as 'innovative, regenerative therapies which combine aspects of medicine, cell biology, science and engineering for the purpose of regenerating, repairing or replacing damaged tissues or cells'. Either a gene therapy, somatic cell or tissue engineered product.

[8] Archived webpage (http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/ab/GTAC/index.htm)

Figure 7: Simplified route map
Showing a simplified version of the Interim Regulatory Route map (shown in Appendix). This representation assumes that the stem cells are intended for human application, that the therapy will be classed as an Advanced Therapy Medicinal Product (ATMP), and that final market authorisation is approved.



Before introducing data gathered during this case study, I shall introduce some relevant regulatory theories. These theories explain some of the different possible ways of regulating new technologies and help us to see where decisions have been

made in the regulation of stem cells. Croley (1998) identifies four different types of regulatory theory to explain how regulations are created, which he believes arise out of the pluralist theory in which interested groups lobby for group interests:

Public Choice Theory – Regulation is seen as analogous to economic markets, where stakeholders (be they public, regulators, interest groups) exchange 'regulatory goods' such as access to markets, price controls etc.

Neopluralist Theory – Interested groups compete in order to obtain the regulations which best match the group interest. Legislators may seek compromises in order to avoid displeasing certain groups.

Public Interest Theory – Three groups exist: the regulators, the general public, and special interest groups. The general public have little influence on the construction of regulations, while the special interest groups may have slightly more influence. Regulators seek to preserve their positions and may attempt to act in what they see as the best interests of the 'misguided' general public.

Civic Republican Theory – Regulatory decisions are made as a result of debate and dialogue between all interested parties, with regulations representing a rough consensus of all parties.

Although Croley's theories explain some of the desires to regulate they do not help us to discuss the different methods of regulating. Chataway et al. (2006) categorise a number of different approaches to regulation, of which the precautionary and reactive methods are most relevant here. The precautionary method of regulating is based on a system set up to avoid potential hazards (Chataway et al., 2006; Harmon et al., 2013). This precautionary principle is sometimes explained as 'do no harm', however in a scientific context it is more accurate to say that it advocates foresight to minimise harm to human health or the environment, and to obtain proof that harm will not occur (Lofstedt, 2003). The precautionary principle is often used in decision making regarding environmental science, and here the aims of the precautionary principle are extended to include 'taking preventative action in the face of uncertainty', whilst also ensuring that a burden of proof is submitted by proponents of change, that other alternatives are considered, and that public views are taken on board (Kriebel, Tickner et al., 2001). Majone (2002) sees the precautionary principle

as becoming a key tenet of the European regulatory framework, but urges caution, citing that it lacks a logical foundation and may result in the distortion of regulatory priorities. The danger of the precautionary principle is in forming a risk averse regulatory system that slows the implementation of new innovations (Foster, Vecchia et al., 2000).

There are many parallels between this regulation based on the precautionary principle and the previous regulation of GM crops. Like GM crops an emphasis has been placed on using social and moral considerations to determine potential 'risks' (Levidow et al., 1996). Tait (2001) writes that the regulation of GM crops based on the precautionary principle allowed judgements based on ethical or moral values to be given a place in the risk analysis of new technologies, and that this can override the use of unbiased scientific assessment (Tait and Chataway, 2003). This certainly appears to have become the norm for debates around stem cell regulation, particularly centring on the use of human tissue. Just like the BloodPharma product the regulators were not debating between a GM crop and no crops, but between GM crops and existing food crops. Similarly to the current blood donation system the advantages of GM crops over existing crops were largely based on expectation - the requirement to introduce new crops before pesticide resistance and other problems caused a fall in food production.

The use of the precautionary principle of regulation has led to a serious of hurdles in obtaining permission for commercialisation of research. In contrast *reactive* regulation sees regulations set up in response to problems which arise from earlier use of a technology (Chataway et al., 2006). When new products are developed the regulations are in place to prevent a repeat of previous problems. These reactive regulations are something which the BloodPharma team will be familiar with, as many regulations within the blood system have been the result of reactions to serious episodes of infections within blood and blood products. The ongoing hepatitis transfer through blood donation from donor to recipient led to regulations banning the use of pooled donations (Starr, 1999, pg.216). HIV contamination in the early 1980's infected 1,227 haemophiliacs in the UK through contaminated plasma

(Darby, Ewart et al., 1995), with the authorities slow to act. The result was the deaths of 85% of those infected. Starr (1999) attributes this lack of immediate action to the reverence given to blood and its symbolic nature as a social gift, rather than a pharmaceutical product. Titmuss (1997) however writes that as well as the trust between doctor and patient there is also an element of trust required between doctor and donor. He attributes infections, particularly in the US, to the way in which blood was no longer seen as a gift. Here blood was often taken from those who had little choice (such as prisoners), or became a product to sell for monetary compensation. Both of these routes made it less likely for donors to be truthful during the pre-donation self-selection process.

Many lessons were learnt from these infection scandals, for example when a blood donor was subsequently diagnosed with CJD all potentially contaminated products were destroyed, at a cost of around £130million (Starr, 1999, pg.342). In the UK blood donation and transfusion is currently regulated under the Blood Safety and Quality Regulations of 2005, overseen by the Medicines and Healthcare Regulatory Agency (MHRA). Using these theories as a basis it can be seen that the regulation of stem cell research has grown out of a number of different approaches to regulation, and that these approaches impact on the regulation of the BloodPharma project. I will now list the key regulatory stages for the BloodPharma project, before looking in more detail at the regulations for blood donation and tissue collection. The following chapter sections will present in more detail the implications for laboratory regulations and licensing of the cultured blood product.

The UK system of blood donation heavily influences the BloodPharma team, many of whom have close links with the Blood Transfusion Services and will be familiar with the regulations which govern blood donation and transfusion. I have previously introduced the reactive nature of blood donation, but many of these regulations are also examples of 'good practice' becoming formalised. Messner's (2009) work on the emergence of Fast Track regulation at the FDA highlights the importance of this social construction in rule making. She draws on examples such as the AIDS crisis to show how regulations of biotechnology do not develop as a set of hard and fast rules,

but are instead born out of the desire of a field to develop good practices. These regulations are often a formalisation of practises already followed informally by those who work in the area, and in many cases turn out to be more adaptive than often expected.

This is the way in which many of the regulations on blood and blood products were originally introduced. A member of the BloodPharma team commented

"*we* [the blood transfusion services] *were there before the regulators.*"

Formalisation of standard practice is seen in the use of the Transfusion Trigger, the haemoglobin level below which it is considered a patient requires transfusion. A level of 100mg haemoglobin per litre of blood became the standard, being easy to remember and high enough to account for inaccuracies in measurement. This trigger value was passed by word of mouth from doctor to doctor, and repeated in almost every medical text book, yet there was no biological basis for this value. Indeed it has been shown that humans can survive blood loss which results in much lower levels of haemoglobin. A 1988 NIH conference sought to confirm the levels of such a trigger, and although they recommended that a concrete haemoglobin level was no substitute for good clinical observation the transfusion trigger of 100mg/l was still accepted (Myhre, 2001; Martyn et al., 2002). Another example of practice becoming standardised is in the amount of blood taken during a transfusion. Again there is little biological basis for this, it was the amount that it was considered a soldier could afford to lose. As many of the BloodPharma team are closely connected with the Blood Transfusion Services they are aware of the introduction of certain regulations linked to practices rather than strict biological markers. In other words they appreciate the malleability of the regulatory system to enact regulations based on clinical use rather than simply imposing a strict framework around which researchers must fit. There does seem to be an appreciation amongst the BloodPharma team that the regulatory system is not hard and fast, but that it is up to the team to provide the data required for regulatory decision making.

A key consideration of regenerative medicine is that the starting research tissue often comes from human sources in the form of embryonic, foetal or adult tissue. The regulation of such starting tissue seeks to balance the use of such material to benefit medical research, whilst also respecting the donor. The two main tissue regulators in the UK are the Human Fertilisation and Embryology Authority (HFEA) and the Human Tissue Authority (HTA). The use of foetal tissue for research purposes is permitted in the UK and foetal tissue is regulated by the HTA, rather than the HFEA. The ReNeuron project uses foetal tissue, and the BloodPharma uses foetal liver tissue in early stages of the research. Foetal tissue is collected after terminations, with strong emphasis on appropriate consent of the women donating the tissue (Kent and Pfeffer, 2006; Pfeffer and Kent, 2007; Pfeffer, 2008).

The HTA was originally set up in response to a public backlash after what became known as the Alder Hey Organ Scandal. In 1999 an inquiry was announced into the removal and storage of tissue from infants, which had taken place at the Alder Hey hospital in Liverpool (Howard and Robert, 2001). It was alleged that between 1988 and 1995 organs had been systematically removed from cadavers and stored without parent's knowledge or consent. Affected parents were outraged that tissue had been taken and stored and that the hospitals continued to be reticent about the quantity of tissues taken. Some parents had up to three funerals for their child as more organs came to light. In the aftermath these parents contributed to discussions on the informed consent process which underpins the work of the HTA. Although the Alder Hey hospital has become synonymous with this scandal (and the media storm that subsequently erupted) the practice of retaining tissue in this way was widespread and accepted by the medical community (Burton and Wells, 2002). The Human Tissue Act of 1961, which sought to regulate the use of human tissue taken from the deceased, had been adhered to in this case, however it was felt that in light of the public backlash that updated regulations were required. These were introduced as the Human Tissue Act of 2004, alongside which was created the Human Tissue Authority (HTA).The updating of the Human Tissue Act placed increased emphasis on consent. Affected parents were involved in the development of new consent

procedures for tissue use, and these parents could be seen as becoming an 'interest group' in Coley's Public Interest Theory of regulation.

The use of embryos in IVF is another example of regulation designed to protect human tissues. The main instigator of the these regulations was the report of the Warnock Committee (Warnock, 1984), set up in response to the birth of Louise Brown the first test-tube baby, which sought to implement guidelines for what was considered a fast paced field. The guidelines resulted in the creation of the HFEA, which could be considered an example of the 'reactive regulation' introduced above, as it was set up in response to the introduction of a new technology. However in this case no problems had arisen, the regulations were designed to protect anticipated introductions of new technology to the field of IVF. The considerations of the Warnock Committee opened up a wider debate on the use of human embryos in research, which is too complex for full explanation here, although for further information see Mulkay (1993), Mulkay (1994), and Parry (2003). The Warnock committee recommended the research limit of 14 days post-fertilisation, after which the embryos must be destroyed. This could be seen as an example of Coley's Neopluralistic theory, with interest groups lobbying for different regulations and legislators seeking a compromise with the introduction of the 14 day limit.

THE EXPERTISE REQUIRED TO NAVIGATE THE REGULATORY SYSTEM AND HOW THIS IMPACTS ON PRACTICE AND KNOWLEDGE

The current regulatory system has been built up in a piecemeal fashion, resulting in a regulatory framework that is comprised of many different bodies and organisations. In this section I shall draw on my interview and observational data to discuss the role of regulatory expertise within the BloodPharma team, and how the regulatory system can be seen to impact on the development of novel stem cell therapies. Stem cell products can vary widely in considerations such as administration procedure, source of cells, and cell purity (Mittra, 2007; von Tigerstrom, 2008). Such diversity is one of the biggest challenges within the regulation of stem cell products as a whole, and the BloodPharma project more specifically. In navigating the regulatory system the BloodPharma team must draw on their own expertise to negotiate the spaces into

which the cultured blood product falls, identifying potential risks and benefits of their particular research. The regulators must also gather together the expertise to fairly regulate novel products which may be outside their normal areas of knowledge.

There are a number of regulatory challenges which arise from the biological properties of stem cells. The bestselling book, 'The Immortal Life of Henrietta Lacks'[9] by Rebecca Skloot (2010) focuses on the use of a particular cell line, known as HeLa. The main premise of Skloot's book is the sheer number of HeLa cells currently in existence, many times the number of cells which made up the body of the original donor. This splitting and dividing of cells is a key ability of stem cells as, unlike whole organs, a stem cell line can theoretically grow and divide indefinitely. The regulatory hurdle of tracking a donated heart, for example, from donor to recipient in a one-to-one model is very different from the traceability required for stem cells. It is already known that cells grown under different conditions can start to exhibit different physiological features, so distribution of cells not only leads to problems of accountancy but also to changes in these cells over time. Webster and Eriksson (2008) show how the 'biological qualities' of the stem cells differ, with markers, characterisation and protocols varying widely between different research groups.

Figure 8: Key Regulatory Stages in the BloodPharma Project

Tissue Collection

Collection of the surplus IVF embryos used by the BloodPharma project is overseen by the HFEA. This regulation is taken over by the HTA at the point that the embryo is destroyed and a stem cell line is created.

Laboratory Work

Overseen by the HTA and MHRA, which have regular inspections of laboratories.

Market Authorisation

Scientific data supplied to the EMEA who scientifically evaluate the safety data for proposed therapies. Once a market authorisation has been granted the product can be licensed for use in patients.

[9] The Immortal Life is a non-fiction book detailing Skloot's interactions with the family of Henrietta Lacks, a poor black woman whose cells were taken without consent and now form the HeLa cell line. The resulting cell line is now one of the most widely used and is present in laboratories across the world.

Much of the work of the UK Stem Cell Bank (UKSCB) is concentrated on achieving culture conditions which ensure the stable properties of cells lines from one generation to the next, seeking to generate a 'reproducible product' (Healy, Hunt et al., 2005) and avoiding contamination (Cobo, Stacy et al., 2005). The UKSCB is therefore a regulatory body which seeks, as well as producing stem cells under GMP conditions, to regulate the biological properties of stem cells. Currently copies of all stem cell lines produced in the UK using human embryos must be deposited with the Bank (Courtney, de Sousa et al., 2011). The UKSCB then acts as a long term repository, allowing other approved research projects access to these stored cells. Only on rare occasions are human embryonic stem cell (hESC) lines permitted to be transferred directly from one laboratory to another. This is quite distinct from the normal pattern of information exchange between laboratories, which often appears to be the result of networking at conferences, emails exchanges and the formation of friendships between researchers; practices which are very distinct from the formal tissue exchanges expected by the regulatory system.

Another similar example of regulations imposing on 'standard' practice was given by the MRC Regulatory Support Centre, which highlighted the problem of researchers collaborating across international boundaries, often unaware that the Data Protection Act prevents the transfer of much relevant data (for example patient information) out of the UK. Incidences such as these are not just about the divisions of tissue but also tell us about laboratory practices and the interactions between researchers and the regulations. Despite the rivalry which does exist between research groups it is also clear that researchers form a variety of networks and collaborations and are generous at helping each other. This includes not only the sharing of knowledge but also tissues, reagents, equipment etc[10]. In this case the regulatory system could be viewed as an impediment to the free exchanges of information and samples that the researchers consider to be 'normal' practice. Stem cells can be shared between

[10] Although I have not been able to gather extensive examples of these practices I have been aware of a desire, especially among academic laboratories, to 'get one up' on the large companies who supply reagents and DNA, often at high cost. Certainly a reasonable amount of the sharing that goes on between laboratories represents an effort to obtain something from a fellow research laboratory which they would otherwise have to pay for.

laboratories because of their ability to multiply and to be stored for long periods of time; however this potential for division is also a key regulatory concern. Whilst pluripotency is an asset for therapeutic development it is also a risk, because if control is relinquished then cells can multiply and differentiate without barriers. The risk of teratomas (tumours that contain a variety of different tissues) is the nightmare scenario of stem cell research and one which the regulatory system is anxious to prevent patients being exposed to. Von Tigerstrom (2008), and Mittra and Tait (2009), cite tumour formation as one of the main safety risks associated with stem cell based products, alongside potential infection (including the possibility of transfer of infectious agents from animals tissue), genetic changes and immune reactions.

Stem cells therefore have the ability to replicate in large numbers and have a double value as both a body tissue and a research tool. In an effort to encompass these different facets, the regulatory system has employed what one of my interviewees termed a 'two pronged approach'. This is that the system attempts to regulate from both a safety and a moral standpoint, with different regulatory bodies having a different emphasis. For example the HFEA and the GTAC are almost primarily concerned with ethics, whilst bodies such as the MHRA and EMA are more driven by safety and efficacy. Brown and Michael (2004) see this as assembling 'regulatory ingredients' in an attempt to envelop novel technologies with some form of oversight. This has resulted in a convoluted regulatory pathway which has been summarised into the Interim UK Regulatory Route Map for Stem Cell Research and Manufacture (Figure 12 included in Appendix). The route map highlights the complexity of the pathway which researchers must navigate and the boundaries at which regulatory organisations meet. For example embryonic and foetal tissue is initially regulated by the HFEA but oversight is passed to the HTA when this tissue is transformed into a cell line. The sheer number of bodies, each attempting to fulfil its own individual remit, leads us to question the boundaries which are placed between different regulatory bodies and between researchers and regulators.

> *"It is a conjunction of processes which were principally designed for other related purposes and they're all coming together, so when you do that you would normally find that* ***there is some degree of overlap*** *and some differences between what different regulators want, partly because*

they have slightly different remits and perspectives and partly because people just do things in slightly different ways." (CS/Med, my emphasis)

This coming together of regulators who oversee stem cell research in slightly different ways, but who both occupy the same regulatory space, is the subject of some confusion amongst researchers in the stem cell field. An overview of the regulatory process in the BloodPharma project is shown in Figure 8. A common theme within the BloodPharma team, which has also been raised by many other members of the stem cell community, is the difficulty of dealing with a regulatory system which does not itself appear to be entirely sure of its own responsibilities. My data shows that the two-pronged approach for regulating stem cell research from both a scientific and an ethical viewpoint is causing an overlap between the remits of certain regulatory bodies. The BloodPharma project currently uses stem cell lines created from surplus IVF embryos, and as such is overseen by the HFEA (whose remit is to regulate the use of sperm, eggs and embryos in fertility treatment and research). At the point at which the embryo has been destroyed and the stem cell line is created the research then falls under the jurisdiction of the HTA. As responsibility for this tissue passes between the different regulatory bodies areas of confusion are exposed, as this researcher from the BloodPharma project describes:

"There has been a lot of grey areas in terms of our raw material, which is embryonic material and then at the point that that embryo no longer exists and we have a stem cell line, at that point we have the HFEA regulating embryonic work but the HFEA regulations stipulating things that you must do with the resulting stem cell line, which they don't officially regulate. ***So there are grey areas like that where one regulator is telling you to do something with some tissue which they don't actually regulate****. I think they are aware of that and are starting to clear things up."* (CS/Lab, my emphasis)

The interviewee is referring to the HFEA wishing to know details such as the eventual application of the resulting stem cell line, even when they are considered by the researchers to be regulating only up until the point at which the embryo ceases to exist. This overlap of regulatory remits between the HFEA and the HTA has resulted in the research teams having to submit the same data to two different regulatory bodies. As part of my data collection I interviewed a member of the HFEA who stated that, in their belief, the HFEA had responsibility for ensuring that the embryos

were treated with adequate respect. The interviewee felt that the HFEA could not do this without a thorough understanding of what the stem cell line would be eventually used for. There seems to be a difference of opinion between the researchers, who believe that organisations such as the HFEA are overstepping their remit, and the regulators themselves who feel that asking for additional data is necessary to properly oversee the use of such starting material. In this case, whilst the submission of data to two different regulatory bodies is both time consuming and costly, permission was granted for the BloodPharma team to create such stem cell lines. The acquisition of other starting material has not been so straight forward, as another researcher explains:

> *"Getting diseased tissue from patients is very, very straightforward in the majority. Normal samples are always difficult. When donors are giving stem cells for bone marrow transplants it used to be that you, with patient consent, could take a little bit extra for research, whereas more recently that was changed and the criteria for collecting was tightened up so that there was a very small window of excess. Which basically meant that we lost all access then to normal research material. We've actually bought in from America normal control samples because we can't get the tissue here."* (CS/Lab)

Here we can see restrictions placed on the collection of adult tissue becoming a major obstacle to those who require samples for research use. The comment that researchers were forced to buy in control samples from outside the UK raises questions of how such tissue collection regulations will impact on the long-term future of the UK stem cell field. Without adequate sources of research material, the UK may become a less attractive option for companies and academic researchers who are looking to develop new cell based therapies.

Regulatory bodies attempting to work outside their individual area of responsibility has been presented in both conference presentations and informal discussions as one of the biggest problems for navigating the regulatory pathway. Similar instances were raised by those I interviewed in the ReNeuron team, particularly with regards to the Gene Therapy Advisory Committee (GTAC):

> *"I think I'm puzzled by their [GTAC] role, and I suspect it's because it's not really very well worked out yet. Normally if you were going through a clinical drug trial development you would get approval for your protocol from MHRA and take that to an ethics committee.* ***Now the ethics***

> ***committee has a role to advise on aspects of ethical concern within a study. But they don't go back to re-review the basic science****. Whereas the experience with GTAC has been that they have concentrated, almost exclusively, on those components which are to do with the basic science. If GTAC require changes in the protocols, well you have to go back to MHRA to seek their approval of the changed protocol. So if MHRA approved the first protocol and then the ethics committee request changes you've got to go back and make sure the changes are also agreed with,* ***so you end up in a loop****."* (O/Med, my emphasis)

Here we have an example that the regulatory authorities do not appear to be sufficiently bounded, and there is often an understanding that the stem cells themselves are 'not right'; they don't fit neatly into any conventional area that we understand. Stem cells have grown out of work conducted in both IVF treatment and in tissue transplantation and engineering, with human embryos considered as 'boundary objects' by Williams et al. (2008) who discuss the different meanings of embryos used in either stem cell research or pre-implantation genetic diagnosis. The distinction here is between destroying embryos in the pursuit of a healthy baby, and using 'waste' embryos for some therapeutic good. Williams et al. show that the same tissue can be considered to have different meaning in different contexts. Stem cells also traverse the acceptable boundaries of species, cutting across animals and human lines with new technologies of human/animal hybrids. Cooper (2004) likens this to 19th century views of 'monstrosities', creations which cut across boundaries and make us question what constitutes 'life' as we know it. The result of this overlapping into different spaces is not just that stem cells move beyond the boundaries of individual regulators, but that they account for only a small proportion of each organisation's regulatory oversight.

> *"The problem with advanced medical therapies is that it intrudes into the space, or it occupies part of the space, of multiple agencies. So all of them, or many of them, have a legitimate interest."* (CS/Med)

The diversity of stem cell products means they are spreading over a wide area of research, which is divided between different regulatory bodies. The interviewee above echoes the words of Brown et al. (2006), who write that stem cells 'traverse the borders between regulated reproduction and transplantation' and also Brown and Michael (2004) who see such technologies as calling for a re-ordering of regulatory boundaries.

As part of this project I also interviewed a number of people involved with the regulatory bodies, including one member from each of GTAC and the HFEA. My data shows that both these interviewees did not feel that the concerns of the research community were justified. We have seen that the interviewee from the HFEA raised the problem that the HFEA cannot guarantee to protect the interests of the embryo without knowing the proposed use of the cell line. A similar argument was made by the representative from GTAC, who felt that an understanding of the development and eventual use of the cell line was vital to GTAC's decision making and any confusion stemmed from the researchers not fully understanding the role of the GTAC committee. We saw in the quotation above the boundary clashes which took place between GTAC and ReNeuron, and this is one hurdle that the BloodPharma team will not have to face as GTAC has now been disbanded. It is however interesting to note that much of this misunderstanding relates once again to the use of contentious tissues in stem cell research. The view of the HFEA that it must protect the interests of the embryo does not sit very well with the HTA, which regulates the line once it has been created and focuses more heavily on regulation from a health and safety viewpoint.

It appears that stem cells are 'messy' because they are both a commercial, scientific product and are imbibed with some form of 'specialness' due to the presence of human tissue. Navigating the regulatory system therefore becomes a story of boundaries, boundaries between existing and novel technologies, between regulations and regulatory bodies and between researchers and regulators. It is at these boundaries where meaning is negotiated (Jones and Graham, 2009) about the validity of different scientific work and about expertise and hierarchy. Much of the boundary work that exists is between regulatory bodies, each of which believes it is following its own legitimate remit, as we saw in the examples of the GTAC and the HFEA. This would appear to be an example in practice of what Shakley and Wynne (1996) refer to as 'boundary-ordering devices', as each regulator attempts to overcome uncertainty by situating themselves on either side of the boundary but attempting a dialogue that takes into account both sides. Such diversity in regulatory

objects must also be accompanied by a diverse body of expertise and such expertise is crucial for navigating the regulatory system. The next section will discuss how the BloodPharma project makes use of differing types of expertise within the project.

Collins and Evans (2002) discuss different forms of expertise in their paper on the Third Wave of Science Studies, drawing on the distinction between the scientists and farmers in Wynne's (1992) study of Cumbrian sheep farmers. What is highlighted here is the difference between the 'formal' expertise of the scientists and the expertise of the sheep farmers gathered from many years of observation and experience on the hills. In this case the scientists often disregarded the 'expertise' of the farmers, while interestingly the opposite appears to be the case within the BloodPharma project. Those with many formal qualifications often defer to the expertise of those with fewer qualifications, but who work day-to-day with the cells and have a working knowledge of the scientific project. Therefore when discussing expertise in this section I refer equally to both formal expertise and expertise gained through experience. The distinctions that I make are instead between the scientific expertise to understand the BloodPharma project, and the expertise required to understand the language and requirements of the regulatory system.

I have discussed previously how stem cells cross multiple regulatory spaces and it is important to emphasise the wide-ranging roles of the stem cell regulatory bodies. The regulation of fertility clinics represents the main bulk of the HFEA's work, whilst the MHRA oversees all medicines and medical devices. In addition to stem cell lines the HTA also regulates the use of human tissue for organ transplants, display purposes, and tissue and laboratory collections. Stem cells therefore represent a minority of each regulator's overall role. On this point it is interesting to note the parallels with Castle and Culver's (2013) work on the regulation of aquaculture in Canada, and the resulting policy and social implications which have arisen from a new technology which does not appear to fit into the existing regulatory framework. In this case aquaculture was overseen by the fisheries regulator, which puts it in direct comparison to established fishing methods but alienates it from the rest of the food industry, which is overseen by a different regulator. As in the stem cell field attempts

have been made to fit this new technology into existing legislation, with the consequence in both cases that the regulatory requirements of this new innovation have become marginalised.

My data show that questions are being raised within the research community as to the appropriateness of these regulators to oversee stem cell research, which can be very different from the other areas which these authorities regulate. For example, as one researcher commented:

> *"the HTA are used to dealing with whole organs and parts of people that are being moved around and are now dealing with stem cell lines which kind of behave differently, and can be split up differently. Rather than having one organ or bits of tissue there can be multiple passages of different cell lines."* (CS/lab)

The researcher is articulating the view that the expertise held by regulatory bodies such as the HTA does not necessarily transfer to stem cells, in this case due to the stem cells themselves, with biological properties so different from those of whole organs. Whilst the HTA has expertise at moving and tracking a whole organ from donor to recipient (normally in a one-to-one model) this expertise does not necessarily transfer to cell lines which can be divided multiple times. Researchers have also commented that the stem cell oversight undertaken by the HFEA appears to be relegated in favour of their 'main' work on regulating IVF clinics, as most of the HFEA's work is centred around its original focus on regulating embryo and gamete use for fertility purposes.

There is an awareness that the stem cell side occupies a small part of the HFEA's remit and has been somewhat 'tacked on' to its overall responsibilities. This did not appear to result in any concrete suggestions of time delays, more a sense amongst the researchers that the HFEA did not really want to be regulating stem cells. Others stated that the HFEA placed too high an emphasis on the moral status of the embryo because its main focus was on fertility treatment. Franklin (2006) refers to the 'double value' of embryonic cells as both a reproductive and a research tool, two values which the HFEA perhaps struggles to separate. Whilst researchers both recognised that the HFEA did an excellent job regulating fertility clinics (and saw the

necessity for laws around the embryo) many questioned the appropriateness of the HFEA to oversee embryo use in research. One researcher commented that more embryos were likely to be created on Lothian Road[11] on a Saturday night than annually in UK laboratories, reflecting the argument that nature is very cavalier with embryos and that there is room for discussion regarding their 'special-ness' in relation to other body tissues. One possible option is that embryos be regulated as any other human tissue, overseen by the HTA.

It is interesting to note that foetal tissue donated after abortions is permitted to be used as a research material in the UK, under strict regulations concerning consent and collection procedures. The use of foetal material attracts much less attention than embryonic material in the public/media sphere. This may be because the use of foetal material is reasonably rare, although the ReNeuron stroke trial uses cells derived from foetal tissue. I wish to draw the reader's attention to the use of foetal tissue because this use is currently regulated by the HTA, not the HFEA. Foetal tissue is also an emotive tissue source that requires strict laws around procurement, yet here it is treated solely as a research material in the same way as any other adult tissue source, disconnected from its double value as a reproductive material. This would indicate that it could be possible for embryos also to be treated in this way, removed from the responsibility of the HFEA and passed to the HTA to be considered a research tissue distinct from any reproductive value.

The question of expertise to regulate extends to the licensing of such products by the European Medicines Agency (EMA). Advanced Therapy Medicinal Products (ATMPs) are regulated through the EMA in order for a wider area of expertise to be called upon. Peer reviews can be called from any of the member states to ensure that an adequate knowledge base is present at any meetings where a particular product is being considered. This peer review is considered to be a crucial process in assessing the scientific robustness of a new technology (Abraham et al., 2000), and shows that the regulatory system is taking note of the wide variety of stem cell products and acknowledges that specialist expertise is necessary to adequately review the

[11] A road in Edinburgh well known for containing a large number of bars and strip clubs.

scientific information submitted. This will perhaps allay the fears of some in the research community who express concern regarding the expertise of those who sit on regulatory committees:

> *"I'd hope that they're open minded enough if not knowledgeable enough, and that the review boards and the discussion boards that they bring together are wide enough to cover all the bases, and that they don't give undue weigh to any single voice."* (CS/Lab)

Whilst the BloodPharma project team understand that the regulators cannot always be experts in every particular field, there is a hope that the bringing together of advisory committees will result in balanced consideration. Of course in order for the regulators to consider the application of a particular research project they must be presented with the relevant scientific data. This data is crucial to explaining the key points of the project to the members of any regulatory committee, alongside the relevant risks analysis, scientific testing, and so on. One criticism of the regulatory system is that there are few guidelines regarding the data that must be submitted; simply that this data must be sufficient for the regulators to make an accurate decision. This results in projects submitting incomplete data or submitting more data than is necessary.

A lot of specific expertise is therefore required to navigate a project through the regulatory system, and the BloodPharma project now employs a specific member of staff to oversee its regulatory submissions (something that looks set to become increasingly common for large scientific projects). This member of staff is the regulatory affairs manager for the SNBTS. A scientist by background, she now works exclusively on navigating projects through the regulatory pathway. The BloodPharma project is a small part of her work, she estimates around 2%, and so she is not always present at scientific meetings or conference calls. Despite this, the team defer to her in most matters of regulation and she is responsible for preparing the majority of regulatory submissions to the regulatory bodies. In interview she mentioned the conflicts that she has between the day-to-day job of the SNBTS and the other research projects that she is involved with, including the BloodPharma project.

> *"BloodPharma's a nice project but it's not our business, do you know what I mean? So if I've got an inspection for our blood business compared with the BloodPharma, and they've both got the same deadline it causes a lot of conflict. So that's a conflict for all of us, the conflict between the day job and the interesting job."* (CS/R)

The members of the laboratory research team sought to delegate regulatory issues to this member of staff or to others on the team who had some understanding of the regulatory issues. Much of this delegation appeared to be due to unwillingness amongst the laboratory researchers to become involved with the minutiae of the regulatory system, mostly due to the length of time that that would be required to read and understand the regulatory documents. The language of regulatory reports was a key area of expertise which the dedicated regulatory person held, and was identified by respondents as one of the main barriers preventing them from becoming more engaged with the regulatory system.

> *"To be honest I think some of the language and the way the documents are written are…do you know what it's like if you read something that you don't even get some of the language, or it's written in a way that you're not familiar with? So it's much harder work to plough your way through it. Whereas I can pick up a protocol for molecular biology and go 'I understand that, that's good' so, we're all really busy and it would take me a long time to plough my way through it and I've got enough to do. I'm sure the regulators would be the same if they tried to read my scientific papers. Because* ***you can only be an expert in a certain area and it's a huge area, it's a whole area of expertise****. I've got an interest in it and I look at what's relevant to our project and get a basic understanding of it but that's as far as I go."* (CS/Lab. Emphasis mine)

Many of the regulatory documents are required to be written in very precise language as they represent the legal Acts which the regulators must enforce. Although places like the MRC Regulatory Support Centre attempt to assist the researchers in understanding these regulations it can be difficult to summarise the documents without losing important parts of the legal responsibilities:

> *"When the human tissue act came out we did some summaries for researchers, just two A4 sides. There are merits to doing that sort of thing, but* ***there is a danger in paraphrasing that you don't include stuff that you need to know****. Or they just read that and they go off and do something and they didn't know that there were other bits that they should have been paying attention to."* (O/Reg. Emphasis mine)

The scientific researchers are experts at their own work and in writing and understanding scientific articles. The regulatory system to them represents an entirely new language and area of expertise, which requires additional training in order to engage with. Regulatory affairs in the stem cell arena therefore seems to be an excellent example of Collins and Evans' (2002) work on different types of expertise. The scientists have formal expertise in their area of research, but struggle with the regulatory affairs which often falls outside this narrow area. Yet their expertise is vital in contributing to the decisions made at a regulatory level, they have 'contributory expertise' in this sense. What they would appear to lack, therefore, is the expertise necessary to understand the documentation rather than the regulatory system itself.

As a consequence of scientists not possessing regulatory expertise they attempt to delegate regulatory matters to those who have experience, and in this case the BloodPharma team have a dedicated staff member to delegate to. For other researchers outside a large research project this can be more problematic. The MRC Regulatory Support Centre (and members of other regulatory authorities who I have spoken to or have heard present at conferences) all comment on the problem of researchers looking to delegate regulatory work to others.

> *"We get a lot of people wanting somebody to write their ethics form for them, but really they are the only person who can write that, because they are the ones that know the project. We can advise them on things they might want to tighten up on, but they know the projects more than anybody else."* (O/R)

Here the problem seems to be that researchers shy away from any interaction with the regulatory system and hope that somebody will take on the job of writing submissions to the regulators. Although the researchers may not be well acquainted with the language of the regulatory system, they are experts in their own projects, as the interviewee above comments. This expertise on the scientific work is required for the regulators to fully understand the data, and so what appears to be lacking here is the translation of this expertise into regulatory reports. This translation is why the BloodPharma project is building up a good relationship with the regulators through their dedicated staff member, and there are also other members of staff on the

BloodPharma team who have an understanding of both the regulatory requirements and the scientific work. The regulatory advisor here has to hold a large amount of 'referred expertise' (Collins et al., 2002), able to understand and coordinate regulatory affairs for big projects, even though they may not possess the same level of contributory expertise as the laboratory scientists. Indeed many of the researchers have commented that students should be given a good grounding in regulatory affairs during University courses, in the hope that there will not be a barrier between scientists and regulators for future generations of researchers.

This early training of scientists to understand the language used by the regulators and an appreciation of what is required in regulatory submission could be key to pushing academic work towards the creation of new therapies. We have seen how navigating the regulatory system requires expertise which, in the case of the BloodPharma project, is undertaken by staff that have a specific role in managing regulatory affairs, and who could be seen to hold 'referred expertise' (Collins et al., 2002). It has been proposed that many academic researchers without this support do not engage well with the regulatory system and that this can have a detrimental impact on the innovation of new therapies. University research across the board is often acknowledged as having poor translation into eventual innovations and economic returns, and this problem is not just applicable to stem cell research (Audretsch et al., 2005).

Particular problems of stem cell research cited by interviewees include the length of time it takes to prepare data for the regulators, with one of the BloodPharma regulatory experts explaining that it can take up to three months to prepare a dossier required for a meeting with one of the main regulatory bodies (it was unclear from the data if this referred to three months of full-time work). What is clear is that this length of time is likely to include the variety of projects on which she has to work simultaneously, the gathering of data from many different scientists, and the reading, understanding and distillation of such data into an acceptable format to present to the regulators. With dedicated staff working on only one project it could be possible to write submissions in less time; however one of the main arguments of the

interviewee is that academic researchers are not 'rewarded' for writing such dossiers. They do not count towards forwarding their career in the same way a journal article would, although dossiers would probably take as long as a peer reviewed article to write. In an academic world which prizes journal publications above other outputs, and interactions with other academics over engagement with industry, this is likely to be a substantial barrier for university based researchers (Bond et al., 2005). Whilst it might be expected that researchers in companies would be more attuned to the implications of navigating the regulatory system, it appears that problems still arise. A common observation from those involved in the regulatory bodies was that developers consistently underestimated the time and money required to bring a product through the regulatory route.

> *"People forget, people always underestimate how long it is going to take, people always underestimate the regulatory requirements and people always forget about involving the regulatory departments soon enough, so that they know all of these additional things. That's a common problem. But not here, everywhere."* (CS/Reg)

Another interviewee also commented on the financial implications of often overlooked aspects of the regulations, such as the keeping of records and documentation which requires space and management. This is consistent with Croley's (1998) account of the costs of undertaking regulatory work, in which he speaks of the often overlooked costs of printing and preparing documentation for agencies, and the expense of obtaining validation data. The reluctance to involve the regulators at an early stage could be attributed to the ongoing boundary work between the regulators and the researchers, the 'them and us' perception which appears in many conversations with the stem cell community. This results in a reluctance to approach the regulators with simple queries or to engage early enough with the regulatory system. Improvements appear to be being made, with more openness from the regulators and additional assistance from places such as the MRC Regulatory Support Centre.

Uncertainties still exist around the late stage EMA regulation and Market Authorisation of the cultured blood project. As we saw in Chapter Four the clinical trials route for the BloodPharma product, and for the stem cell field in general, is yet

to be established. The EMA considers its central responsibility to be the protection of human and animal health, and we may see that the presence of an already established blood donation system makes regulators more cautious to introduce a novel therapy. Throughout the project the BloodPharma team have been working at GMP grade wherever possible, aiming to lessen future hurdles which could arise from doubt about the provenance of the cells. It is clear that large uncertainty still surrounds the step from the laboratory to the clinic, and Rutter and Plomin (2008) argue that strengthening basic science will never be of benefit unless the translation of that basic science from bench to beside is also addressed. Indeed this translation should be of key importance to the stem cell field, where large amounts of potential products have failed to translate into many useable therapies (Brown et al., 2006; Brown et al., 2006). This lack of translation is also having a detrimental impact on investment in stem cell companies, with the uncertainty of the regulatory pathway and the ambiguity of IP potential being cited as being as important as ethical or safety concerns to investors (Giebel, 2005). It is easy to see how the regulatory system can impact on a company, for example with ReNeuron:

> *"We've also found that GTAC have found ways of parking things so that carefully worded responses have had the effect of stopping the regulatory clock ticking. Which has been a frustration, particularly to ReNeuron,* ***who I dare say probably see their money evaporating with every passing day that things don't get going****. And that's been frustrating, and I think somewhat counter to the intention of the overall framework for approving clinical studies. These timelines were set up in order to ensure that things went through in a fairly clearly defined timeline."* (O/Med, emphasis mine)

There is a requirement for staff with new skills dedicated to translational research (Littman, Di Mario et al., 2007), and this is articulated by the BloodPharma team in their call for more researchers who understand both the scientific work and the regulatory implications.

The slow speed of translation can be seen as having a detrimental impact on patients and researchers in the UK setting. During interviews some respondents commented that the UK was fast losing its advantage as a primary driver of stem cell research, with researchers who had been initially attracted by the regulatory regime in the UK now seeming disillusioned with the process. The rising powers of India and China

were mentioned regarding the potential production of the BloodPharma product, echoing Salter et al. (2007) who see India employing new models of innovation to attract stem cell investment. We have seen that expertise plays a significant role both in the ability of stem cell regulators to understand the science and in the ability of researchers to navigate the complex regulatory system. Although the laboratory scientists involved in the BloodPharma project often delegate interactions with the regulators to other team members it is these scientists who are the experts on the unique properties of their own research product. The next section will examine in more detail the regulatory questions which arise when considering the cultured blood product.

BLOODPHARMA AS A PRODUCT IN THE CONTEXT OF THE REGULATORS AND SPECIFIC RISKS

In this section I will concentrate further on the cultured blood product itself to explore how the project team considers the specific risk issues associated with this project. After completing the early stage scientific work, the BloodPharma project will need to negotiate market authorisation through submission of data to the MHRA. The uniqueness of the cultured blood product makes it a test case for the regulatory system, as this BloodPharma researcher explains:

> *"We've always argued that red cells are **an ideal test case** for all of this because they're enucleated. And therefore we should be able to use genetic manipulation and we should be able to use embryonic stem cells because we're mitigating the risks in the end product. However, what we're never going to be able to get around is that the level of purity is going to have to be ludicrous." (CS/Lab, emphasis mine)*

As the eventual BloodPharma product will contain no nuclei, techniques such as irradiation can be used to destroy any residual DNA in the cells (as the researcher is referring to in 'mitigating the risks'). RBCs are the only cells in the body not to contain a nucleus and so the researcher is commenting on the unusualness of this product amongst other cell therapies, as the presence of DNA is normally a major risk of stem cell therapies. Cells with nuclei will contain DNA which could be transferred from donor to recipient and can also allow the cells to multiply, potentially causing teratomas. This risk mitigation however depends on the

enucleation techniques working for every single cell, and the BloodPharma team will have to transfuse thousands of cells into a potential recipient. The BloodPharma team is therefore interested to see how the regulatory system will react to this product, which does not fit previous risk models of stem cell therapies.

The area of stem cell based products covers a vast number of potential therapeutics with varying biological properties and accompanying risk factors (POST, 2004). The BloodPharma team must ascertain which particular parts of the project would be of interest or concern to the regulators.

> *"The reflection paper on Stem Cells from the EMEA, that basically tells you, here's your risky bits, and what we need to do is go 'ok, that's risky' and from that reflection paper we built what we thought we needed to test."* (CS/Reg)

The Scottish National Blood Transfusion Service already has a good record of interaction with the regulators, due to its development of other cell based products such as corneal bandages, and is therefore able to draw on this experience to identify key sticking points in the regulatory pathway. As the interviewee above explains, knowledge of potential risks allows them to tailor data collection to give regulators a more accurate risk profile for their individual product.

In the absence of long-term use of stem cell treatments (other than bone marrow transfusions) the comparison of one potential therapy with another is a useful tool for assessing risk. Much of the discussion with the BloodPharma team did not involve risk data for the BloodPharma product specifically. Instead they mentioned that it was more risky than the corneal bandages (which use partially differentiated cells) but less risky than the ReNeuron project which injects stem cells into the brain, less risky than treatments which involve cells growing for long periods, but more risky than treatments which require lower number of cells.

> *"To a large extent I'm really happy that Geron[12] are running that gamut ahead of us, because their cells are nucleated and ES derived, so they are going to have to deal with a lot of what we do."* (CS/Lab)

[12] Geron are a US based company that were developing a stem cell product to regrow the spinal cords of paralysed patients.

Here the researcher identifies one of the ways in which uncertain risks are debated, by comparing the risks of their project with another that has navigated the regulatory pathways before them. In this case the team were hopeful that Geron, which is seen as having a 'riskier' product due to the nucleated cells, would be ahead of them in the pathway. In this way the BloodPharma team can gain some idea of what risks and benefits were picked up by the regulators, and what data Geron had to submit. Unfortunately the Geron trial was stopped in 2011, so the BloodPharma team must look elsewhere for test cases of the regulatory pathways.

The researchers here seem to be employing what Sadler and Zeidler (2005) refer to as 'informal reasoning', a way of attempting to work out problems without apparent solutions by debating pros and cons, causes and consequences, and so forth. Kahlor et al. (2002) also draw upon informal reasoning when studying risk estimates amongst residents after a water contamination incident. Sadler and Zeidler identify a number of considerations which are taken into account during such informal reasoning: Personal experience, emotive considerations, social considerations, morality, and perceptions of complexity, which I found mirrored in data gathered from the project team.

In understanding the regulatory concerns around the BloodPharma product, members of the team drew on their own personal experiences of working in other sectors or in other countries. For example one interviewee had been working in the area of gene therapy when trial side-effects had stopped the scientific field in its tracks. Another had worked in the US and articulated how glad they were about the balanced regulatory system employed by the UK, especially in comparison to the religiously funded academic institution where they had previously worked. The researchers used past experiences to make judgements about the risks associated with stem cell products and the need for regulation, for example by remembering instances of past problems such as major blood contamination. They used these as examples of why it was so important that stem cells were well regulated. This appears to be similar to results found by studies such as Siegrist (2000), who found that trust played an important role in the perception of the risks and benefits of a novel technology.

Fischhoff et al. (2012) also found that perceptions of risk amongst a group of Americans were based on past personal experiences, although the study concentrated on terrorist risks rather than novel technology.

The scientific team occasionally talked about the emotive considerations of their work, drawing upon the desperate need of patients or those who have been affected by previous drug safety or regulatory failures.

> *"The patients have a desperate need, but the clinician has to safeguard themselves too, unfortunately."* (CS/Reg)

> *"So I think we have a very willing public and a very trusting public, but then things like Alder Hey have damaged it."* (CS/Lab)

Throughout the project it has been evident that the BloodPharma team do engage on a very personal level with the expected outcomes of the research. Although some have commented that they do not see this project as perhaps ever reaching the clinic, and view it more as an academic exercise, for the most part the researchers seem to envision the long term goals as helping those patients who will most benefit from the cultured blood product. Some who had experience of working with patients with blood disorders drew on the terrible suffering which these patients and their families experience. Others talked of patients going abroad for therapies and their desire to be able to offer safe and appropriately tested therapies here in the UK. The researchers draw upon social considerations to explain why the innovation of a cultured blood product is necessary.

> *"There might be situations where you really want to be absolutely sure that you really have got a very clean source, so maybe in transfusions, for you know, children or something. Third world as well, I mean there's no blood transfusion in the third world at all, where, you know, there isn't the source."* (CS/Lab)

The use of cultured RBCs in developing countries or for minority populations within the UK is one of the first targets of the cultured RBCs. Members of BloodPharma team saw themselves as having a social responsibility to help those who currently do not have access to a safe blood supply.

> *"So yeah, Italy, Spain, most of bible belt America, there's enormous tranches of the world that wouldn't consider it still now, let alone if it's*

the only option, so no we're going to have to find a different source for it eventually." (CS/Lab)

Here we can see that the interviewees also had an understanding of the social problems that may occur should the cultured blood product be available to the wider population, for example those who would have religious objections to products made using embryonic stem cells. It was interesting that when questioned why stem cells should be regulated that the researchers drew on moral reasoning, rather than purely safety.

"I start to get a bit wobbly with ES cells when you get to producing gametes, I'm not quite sure how well regulated that end of things is because it's not something I do. That starts to make me uncomfortable." (Cs/Lab)

"And the early bone marrow for heart failure and the heart attack trials were frankly scary, to my mind that was just, experimentation, as you would do on mice but in humans. I was not comfortable with all of that stuff I have to say." (CS/Lab)

They spoke of earlier trials gone wrong or of the potential for people to be exploited by unscrupulous clinicians in other countries. Whilst most of this does of course come back to the safety of the cells it was evident that the researchers also drew on their own moral codes about safety and protection, and appropriate use of cells in clinical trials. This use of morals amongst scientists brings to mind the wider literature on responsible innovation, and the argument for increased self-regulation amongst the scientific field rather than a reliance on top-down frameworks (Hellström, 2003; Owen and Goldberg, 2010).

Finally we can see that the researchers are very aware of the complex nature of regulating cell based therapies and the challenges that occur in navigating the regulatory pathway.

"I think its complex, and I think the reason it's complex is because it hasn't been designed by one hand, it's evolved, so there's a legacy of existing law and regulation and regulatory bodies, all of which come to bear on these new, very advanced cellular therapeutics." (CS/Med)

Those with previous experience in either blood or pharmaceutical industries talked about the nature of stem cells requiring a multifaceted regulatory system. There was

an awareness that the regulations have been built up over time and were perhaps no longer fully appropriate for this fast- evolving field of stem cell research. Although Sadler and Zeidler based much of their work on informal reasoning on the study of science students it can be seen that such reasoning processes are also used by those who are much more advanced in their careers, and helps them to make some form of sense of the risks associated with stem cell research. Although this use of informal reasoning is unlikely to impact the regulatory system in the way Jones and Graham (2009) call for, it is interesting to see the impact of such informal reasoning on the views of researchers in the BloodPharma product towards the risk/benefit balance of their own product.

The difficulty of guiding the BloodPharma product down the correct innovation pathway lies in balancing both the requirements of the regulatory system with the constraints of the biological processes. The team can effectively be seen to have two pathways to navigate, both of which require forward planning of months or even years. This forward planning makes the job of the BloodPharma team in navigating the regulatory system that much harder, as the biological processes are so intertwined that tweaking a small amount of the techniques may require large amount of background work. In order to prevent unnecessary cost (both financial and in time/manpower) the team must look ahead to anticipate future hurdles.

> *"What you do now is absolutely critical because **it is part of the provenance of the cells**, so you might do something now and have a judgement on it in five years where the regulator says 'well actually we don't like that, you need to go back and start again' and we have seen that in other fields. So that's I think our purpose, we already have a very close relationship with MHRA and HTA and to a lesser extent HFEA and that's our purpose of engaging with those regulatory colleagues at a very early stage, because they need to understand what we're doing so that in five years it doesn't come as a surprise to them, they don't say 'well actually if you have just asked us we would have told you to do it this way'. Because **they're learning as well**, it's important to understand, you know it's an evolving field and they are not starting from a well established base in that respect."* (CS/Lab. Emphasis mine)

The interviewee here is articulating one of the main concerns for any stem cell product seeking future regulatory approval. Producing a stem cell product is not the same as the batch processing commonly used in other industries. It is not possible to

start again easily from scratch, as the process may be based on cells which are derived many years before the product itself has been approved. A lay example would be sourdough bread, where bakers often keep the yeast culture in use for many months or even years, compared to one-off batches of normal bread rolls. The provenance of the cells is therefore a key concern and researchers must anticipate regulatory requirements many years before the regulators themselves have articulated these. Throughout the project the researchers employed what could be termed a 'belt and braces' method (being extra cautious and taking multiple steps to ensure that the cells would be appropriate for future use), for example deriving cells at GMP which did not need to be (and thereby incurring greater research costs) so that they had covered all bases and reduced the possibility of being asked to redo work many years down the line.

There is also the argument that it is potentially easier to run the entire system at GMP than to have a separate GMP and non-GMP research stream. Running one system allows all the researchers in the team to work to the same protocols.

> *"We would make small choices, so for example if there was a clinically used reagent available rather than a bog standard research grade one we would start with the clinical reagent, just to build in that bit extra."* (CS/Lab)

The respondents were very clear, however, that they would not attempt to do something for the sake of regulatory ease unless it also made good scientific sense. For example the removal of cell feeder layers, although a regulatory concern, would also have affected the scale-up potential of the project. This shows that the BloodPharma team is seeking to do 'good science', which in some cases may be going above and beyond what the regulators ask for. In other cases this may result in the BloodPharma project having to fight for its right to carry out the best science it can, even if this goes against the advice of the regulatory system. This occurred in the ReNeuron project where the doctors had to fight against the regulators who wished all patients to have immunosuppression. Believing it was not necessary for their study and could harm the patients the medical team refused to accept the regulatory advice and instead spent time gathering extra data to convince the regulators that immunosuppression was not required. Their submission was accepted

and the trial is continuing without using immunosuppression. This is another example of scientists seeking to carry out the responsible innovation discussed earlier, above and beyond the stipulations of the regulatory system.

I previously introduced the precautionary method of regulating, where 'doing no harm' is considered to be the primary requirement. This is an important consideration to the BloodPharma team, as what sets this case study apart from other stem cell therapies is that it is seeking not to implement a new therapy but to find an alternative source of producing an existing therapy. This situation of simultaneously promoting the novel cultured blood product whilst still recruiting blood donors for the current system makes this case study unusual amongst the wider stem cell field (as will be discussed in more detail in Chapter Six).

> *"I think the issue is would you take proper blood or BloodPharma blood, that's the risk the regulators see, forget what the patients see. We are in the advantage and disadvantage, and we did say that to the EMA, that we have a really well known product to compare it against. And we will have to prove that our product is as safe, or safer, or more efficacious, than this."* (CS/Reg)

This quote shows that the difficulty of regulating the BloodPharma project using a regulatory system based on the precautionary principle is that this risk of harm must be measured not against the risk of no treatment, but against the risks of the existing treatment.

Donated blood is still considered to be both a tried and tested and comparatively safe treatment for the majority of patients who require blood transfusions. Stainsby et al. (2006) put the total adverse events associated with blood transfusion from 1996-2004 at around 10 per 100,000 components issued, with Transfusion-Transmissible Infection accounting for 0.4 per 100,000. Given the attention placed on such adverse events the reality is that modern transfusion is statistically very safe. The argument given by members of the BloodPharma team and other proponents of new blood technologies is that although the current relative risk is very low this is based only on known risks. The blood services can only test for diseases for which there are tests available and that are known to be transmitted through blood transfusion. It is considered that underlying problems such as vCJD may prove to be future crises

through symptom-less ‘silent carriers’, who infect others through transfusion because neither the patient nor the medical community are aware of their disease until many years later (Llewelyn, Hewitt et al., 2004; Wallis, 2009). The burden of proof falls on the scientists and regulators to ensure that the new product is not just safe, but that it is as safe as the existing product. The team will have to show that the regulators are justified in allowing an established product to be replaced with a new, potentially riskier, innovation. A key factor in the precautionary method of regulating is that other competing innovations must also be considered.

There are a number of global competitors to the cultured blood team with the main competitor considered to the laboratory of Luc Douay (Paris) (Douay and Giarratana, 2005). This competition is likely to be of less interest to the regulators as such similar innovations will all carry broadly similar risks to the BloodPharma cultured blood project. What, however, may be of interest is competing technologies that offer a replacement for the current blood donation system but which offer different, or reduced, risk profiles (for example chemical based RBC substitutes). There is also a growing movement around ‘bloodless’ techniques, which could significantly reduce the requirement for donated blood. These techniques were pioneered in hospitals in the US as a method of treating Jehovah’s Witnesses, who refuse to accept any blood or blood products. Such hospitals have been extremely successful at minimising the amount of blood used by patients and have shown positive patient outcomes. Techniques to minimise blood used during surgery require a co-ordinated approach across different clinical teams, including pre-operative, surgical and post-operative care (Rees et al., 1996).

This may have advantages, for example by allowing the regulators to concentrate solely on the risk vs. benefits for those patients who will still need regular blood transfusions or whose blood loss through trauma is beyond the help of bloodless techniques. Concentrating on specific target groups may also be beneficial for the design of clinical trials, where specific disease profiles can be studied ahead of assessing safety and efficacy for the wider population. For eventual ATMP regulation the benefit of the product being targeted at those with specific disease is

the possibility to open up alternative routes to clinic, such as Hospital Exemptions, which allow a product to be produced and used in small quantities on a named patient basis. It is evident that the BloodPharma cultured blood product itself has unique properties which make the relative future risks difficult to determine. The method of regulating using the precautionary principle may have a detrimental affect on the licensing of such a product, given the presence of an already established blood transfusion model. The difficulty for the researchers is in anticipating the questions and concerns of the regulators which may be raised further down the line, and ensuring that scientific robustness is built in to cope with future problems. Only as the cultured blood project moves further down the regulatory system will it become apparent whether the expectations of the researchers have been accurate.

CONCLUSION

In this chapter I have used empirical data to analyse how the regulatory system shapes the activities of the BloodPharma team and the development of the cultured blood product, and what this can tell us more generally about the regulatory system for stem cell products. We have seen how stem cells are complex products capable of causing harm to patients, and that their use as a clinical product is therefore tightly controlled by a number of different regulatory bodies. These regulatory bodies have grown out of previous incidences in the scientific field, for example the Alder Hey Scandal. Theories of regulation were also introduced, as was the use of the precautionary principle. Drawing on the work of Messner (2009) we saw that many of these regulations were a formalisation of already existing norms and practices, and in the case of the BloodPharma project this is closely linked with the wider regulation of blood transfusion. The use of embryos and foetal material was also discussed in the context of the regulation of this starting tissue, which often draws upon ethical or moral judgements.

The complexity of the regulatory system for stem cell research in the UK requires specialist knowledge and expertise in order to navigate. Stem cell research crosses numerous boundaries and the overlap between regulatory bodies has been seen to lead to confusion regarding the specific remits of different regulators. Using

interview data from the BloodPharma team and others in the field, for example the ReNeuron trial, we have seen how this confusion impacts on the development of new stem cell products and therapies, for example in leading to the resubmission or duplication of data, and increasing financial pressure on companies. Expertise within stem cell regulation is required not just by the researchers but also by the regulators, who are seeking to oversee a fast paced research area where much of the specific knowledge is held by the researchers themselves, in what can be seen as formal expertise. The transfer of this knowledge to the regulatory bodies requires specific knowledge, which in the case of the BloodPharma team is undertaken by a dedicated staff member, who possesses referred expertise in their ability to manage the regulatory affairs of the project. The requirement for such a staff member emphasises the knowledge gap which exists for most scientists, who are unable to engage fully with the regulatory requirements, and who see this as developing from a lack of time and also a lack of expertise to engage with the specific technical language used in many regulatory documents. This development of regulatory understanding highlights an area of specific skills which should be developed further by universities seeking to train future researchers.

The BloodPharma team has argued that its product is an ideal test case of the regulatory system, due to its unique biological properties. The data gathered here has shown that there is still a large amount of uncertainty related to these risks and the future regulatory trajectory of the product. The use of the precautionary principle in regulation is of importance to the BloodPharma team, which must ascertain that the product is safe and efficacious compared to the existing product of blood transfusion from human donations. Here we have seen that the team use informal reasoning to make sense of the complex risk profile of the product, by comparing it to other stem cell products, and also by drawing upon moral and social considerations. The foresight necessary to ensure the provenance of the cells is evident in the decisions which the team make, such as which laboratory reagents to use, although it is clear that only time will tell if this foresight proves to be correct.

CHAPTER 6: PUBLIC ENGAGEMENT IN THE BLOODPHARMA PROJECT

INTRODUCTION

During the three years of the Wellcome Trust funding the BloodPharma team has been heavily engaged in public communication and outreach. In this chapter I will explore how this outreach has been undertaken, and focus on the responsibilities and experiences of the scientists themselves within this work. As part of my data collection I took on the role of participant observer at many of the project's outreach events, and experienced first-hand the challenges and rewards of talking to attendees regarding the cultured blood project. Whilst the literature around public engagement has moved from a focus on the lay public, to attempting to understand more about the motivations and frustrations of the scientists that perform outreach work, such studies usually take the form of interviews or questionnaires. Therefore the opportunity to take part in engagement alongside the scientists has provided insights into their personal and professional feelings about public outreach.

This chapter will address the following research question:

What are the main drivers and motivators behind the BloodPharma team engaging with public outreach, and how do the scientists respond to their own role as public communicators?

The first section of this chapter will use data drawn from the BloodPharma case study to uncover and assess the drivers of outreach. I will analyse this in the context of past controversies, for which I will draw on relevant literature. This will include the backlash against the introduction of GM crops, as well as Tait's work on the repercussions which this and other incidences had on the introduction of the precautionary principle. This highlights one of the key motivations for doing public outreach; that is to mitigate future public and/or interest group challenges to novel technologies. Perhaps the primary motivation for the BloodPharma team specifically in public outreach has been pressure from the contributing universities, and I will therefore examine literature around the wider pressure for scientists to move out of

the laboratory and into the public space. This includes the call for academics to justify their 'Broader Impact Criteria', and the critiques of measuring what constitutes broader impact. The final motivation considered is the more pragmatic one of patient and doctor acceptance. This acceptance is of vital importance to the use of a new product in clinical use, especially considering the purchasing power of the NHS. To look further at the acceptance of new therapies I will draw on past surveys related to blood and blood substitutes, as well as work around direct-to-consumer advertising of prescription drugs.

For the second section of the chapter I will explain the types of outreach which the BloodPharma team have undertaken, and assess the three key messages that formed the backbone of the public outreach. These are the need for blood, the similarity between cultured and *in vivo* blood, and situating the BloodPharma project within the wider stem cell field. In response to a conference discussion around the BloodPharma project I shall also consider what public engagement means in the context of multi-million pound scientific projects. I question what the new introduction of 'engagement' over 'outreach' or 'communication' hopes to achieve, and how far it is practical to hope that public opinions will change scientific pathways.

In the third and final section I will focus on the role of the BloodPharma scientists within the outreach work. For many this represented a step out of the laboratory and into a communications role that they had not previously been familiar with. Challenges included communicating complex scientific work to a lay audience, as well as the hard physical work which is an often unseen side of such communication events. Coupled with this is the individuality of the BloodPharma project in already having an accepted product in blood donation. This represents a double-edged sword for the team, on one hand giving them something which is already familiar to the public, whilst on the other preventing them from justifying some of the reasoning behind the BloodPharma project. This is due to the requirement that any outreach must not adversely affect the willingness of people to donate, or to receive a blood transfusion. Therefore factors such as the requirement for cultured blood to

overcome infection rates have to be down-played. The team has also struggled with the media portrayal of the project, which often tout the cultured blood product as 'synthetic', despite the best efforts of the scientific team.

KEY DRIVERS OF PUBLIC OUTREACH AND THE EXPECTATIONS OF THE BLOODPHARMA TEAM

Public understanding of science is now recognised as increasingly important in promoting the acceptability of new innovations. The BloodPharma project uses human tissues that are considered to have emotive value (embryos and blood), and brings together branches of research which have previously been of concern to the public. In this section I will use the literature to discuss past incidences of public reactions to technology, highlighting why the BloodPharma team has prioritised early engagement with the public. I shall then discuss the requirement of funding bodies to carry out public outreach, and the need to engage early with patients and health care providers. Before addressing some of the past controversies it is necessary to explain the different uses of words such as 'outreach', 'communication', and 'engagement', which I shall use throughout this chapter.

At the start of the growing trend towards making the lay public more aware of science the terms 'outreach' or 'communication' were commonly used. However in light of an increasing understanding of the two-way process of feedback between scientists and the public the terms 'dialogue' or 'engagement became more widely implemented. This change is attributed to an understanding of the public deficit model – the idea that the public became treated as uncomprehending vessels to be filled with knowledge, and that any resistance to a new technology therefore stemmed from a lack of knowledge on the part of the publics (Sturgis et al., 2004). I have throughout this chapter referred to 'communication' or 'outreach' more than to 'engagement', because I believe that the set-up of the BloodPharma model does not encourage two-way engagement but is instead focused primarily on education. I shall later explain this in more detail as it relates to the BloodPharma project.

The public reaction to Genetically Modified (GM) food crops has been one of the most publicised incidences of resistance to the introduction of a new technology, with protesters often gathering wide media attention with their attempts to destroy fields of GM crops during scientific trials. This mobilisation of protest groups or 'direct action' groups became synonymous with this reaction against GM technology (Grant, 2004) and highlights the power of public reactions to be taken into account in regulatory decision making. Writers differ in their reaction to this public input, with Burke (2004) writing that the turn against GM technology has been based primarily on public fears and concerns, rather than on scientific data, whilst others such as Majone (2002) argue that a lack of scientific evidence that something is unsafe is not the same as evidence of safety. The British Medical Association reported no evidence that GM crops are unsafe, although urged caution given that the long-term impact of GM foods on human and environmental health had not yet been established (BMA, 2004). The requisite for evidence of safety (rather than a lack of evidence of un-safety) is a key tenant of the precautionary principle method of regulation, which was initially introduced after public reactions to pesticide regulation, but has also become commonly used as a method for regulating GM crops.

Tait (2001) sees this as highlighting a major weakness in the precautionary method of regulating, that it takes into consideration elements other than scientific data, for example ethics. For GM crops it appears that public reaction has been one of the primary drivers for the slow introduction of GM crops in the UK (Tait and Chataway, 2007), and the rest of Europe, compared with the US and China. An incidence such as this highlights disparities between the scientific community and the lay public regarding risk based decisions. Wynne (1992) explains this as the 'real' risk seen by the scientists, versus the 'perceived' risk seen by the public. As 'perceived' risks were thought to be based on misunderstandings (the public deficit model) or inaccurate information, scientific outreach or public engagement was therefore considered to allow the public to form a more accurate view of the actual risks. In other words public outreach was seen as a way of restoring 'public trust' in science.

Stem cell research has previously garnered a share of this scientific mistrust, with the use of embryonic stem cells in research becoming the subject of much public debate, especially involving some of the major religious and moral groups. As a consequence of such debates the eventual restrictions placed on research (for example the 14-day limit on embryo use), at the recommendation of the Warnock Committee (Warnock, 1984), were seen as representing a compromise between the pro- and anti-reseach sides. Stem cell technology also crosses boundaries into areas such as xenotransplantation, a technology which Fox (2005) describes as incurring a 'deeper cultural unease about bodily mixing and rejection', and which Cooper (2004) sees as returning to the nineteenth century ideas of 'monstrosities'. Bates et al. (2010) identified public unease around stem cell research to be due in part to a feeling of distance from the scientists and a belief that the public would be kept oblivious of advancements in this technology. Much of this unease was related to a lack of awareness about the tight regulatory system, leading to concern amongst the interviewees about 'rogue' scientists having free reign to experiment as they saw fit. This was especially related to the use of human tissue in research, as stem cells bring with them the emotive issues associated with the use of embryos and other tissue, which has made them a popular topic both for social science researchers and the media. There is a broad selection of literature on the public debate around embryonic stem cell use, for example Warnock (1984), Mulkay (1993), Mulkay (1994), Parry (2003), Devolder (2005), De Sousa et al. (2006), and Lovell-Badge (2008).

In an earlier chapter we saw how the Alder Hey Scandal (in which the organs and tissue of deceased children were retained without parental consent) was a major incident which created a breach of trust between the scientific/medical community and the public. The public backlash has been reported as 'demonising' the profession of pathology (Burton et al., 2002) and was instrumental in changing the guidelines for post-mortem retention of tissues. That the guidelines were changed in response to this public outcry, and the associated media attention, is a testament to the power of public opposition (Bauchner and Vinci, 2001). Indeed it is an incident which the

BloodPharma team have referred to, for example in this previously used interview quote:

> *"So I think we have a very willing public and a very trusting public, but then things like Alder Hey have damaged it."* (CS/Lab)

The Alder Hey affair has become synonymous with the idea of misuse of human tissue, despite the fact that the retention of such organs, or parts of organs, was considered standard practice, and as such was happening in other hospitals across the country (Burton et al., 2002).

The BloodPharma team has been especially conscious about engaging early with the public as the project uses both embryonic stem cells and blood, both of which can garner very emotive reactions. Whilst the public unease around the use of embryonic stem cells has been much discussed it should not be forgotten that, for the BloodPharma project, the issue of emotive attachment to blood and blood donation represents an equally challenging subject for public engagement. Blood transfusion technology itself was essentially halted for almost 100 years by the public outcry over Denis' work in the 17th Century (Brown, 1948, pg.7), and there appears to be an attachment to blood, especially to 'real' blood, which creates unease about alternatives.

A study carried out by Fleming et al. (2007) into the risks and ethics associated with different blood types and substitutes found that those studied had a preference for donor blood, being regarded as the most effective, most ethically acceptable and least 'risky'. This was followed by chemical-based substitutes, bacteria grown substitutes and finally bovine derived substitutes, which were seen as being the most risky, least ethically acceptable and least effective. Interestingly perceptions of risk correlated with both ethicality and effectiveness for all of the options. The study shows that despite the infection scandals which have been associated with human donor blood, this is still seen as the preferred option by those who were interviewed. This also correlates with Ferguson et al. (2008), whose study found that chemical substitutes were seen as being somehow substandard to 'real' blood. To ensure public

acceptability of the cultured blood product the BloodPharma team is embarking on an outreach campaign which could be seen as an attempt to 'market' the product. This was also considered by Ferguson et al. (2008) who suggested that alternative blood products would require more effective marketing than had been seen with synthetic blood products, such as HBOCs. It is hoped that by making people more aware of the potential of alternative blood sources that these associations of risk or ethical dubiousness can be reduced. Not considered by Fleming et al. is the attachment that the public have to blood *donation* due to the principle of altruism and gift giving, which forms the primary subject of Titmuss' (1997) book. This is a driving force behind the blood transfusion services in the UK and many blood donors are very attached to giving blood, as will be discussed in more detail later in this chapter.

Recent years have seen a turn away from a culture of individual scientists working in isolation to a focus on the broader impact of scientific work. In the United States an educational reform in 2001 led to the creation of the 'No Child Left Behind Act', which prioritised reading, maths and science subjects (Moskal, Skokan et al., 2007). An integral part of this new reform was the involvement of higher education establishments in engaging with pupils of pre-college age. Academic establishments were urged to go beyond research and publishing, and to incorporate also 'discovery, integration, application, and teaching' Boyer (1990) in Moskal et al.(2007). Other funding bodies have also begun to push for further outreach to be done by higher education establishments. Since 1997 grant proposals to the US National Science Foundation (NSF) have been required to include an assessment of the broader impact of the proposed research (Holbrook and Frodeman, 2007)[13], and universities more generally are coming under increasing pressure to justify their public funding (Bond et al., 2005).

Attention is therefore increasingly focused on the 'broader impact criteria' (BIC) of academic research. Critiques of BIC as a funding criterion are that it relies on a linear

[13] More specifically proposers and reviewers were asked to judge (1) What is the intellectual merit of the proposed activity? and (2) What are the broader impacts of the proposed activity? Holbrook and Frodenman (2007).

model of innovation, an assumption that a research project will necessarily lead to proposed goals which will then in turn have a beneficial impact on society (Frodeman and Parker, 2011), and that it also requires peer reviewers to determine what is considered a broader impact (Bozeman and Boardman, 2009). The aim of much of this work on BIC is to move away from the idea of the academic in an 'ivory tower' (Bond et al., 2005) and towards the image of scientists engaging more with the lay public. This has called for more investigation to be done, not on the views of the public, but on the views of scientists and academics as they go about public engagement. A report by the Wellcome Trust (2001) found that scientists believed public outreach to be beneficial. Those interviewed, however, saw a lack of public understanding or interest, and a reliance on media output, as being some of the major hurdles to the communication of scientific work. Whilst over a half of those interviewed had been involved in some form of communication, few had any specific media or communication training and many felt ill-equipped to talk about the ethical or social aspects of their work (Trench and Miller, 2012).

Other studies have shown similar results, for example Mathews et al. (2005) who interviewed geneticists about their role in public outreach. For the BloodPharma project involvement in public outreach was initially proposed by the University of Edinburgh, which wanted a research project to submit for a chance to exhibit at the prestigious Royal Society 350th Birthday Exhibition, and thereby promote the broader impact of research being undertaken by the University of Edinburgh. The BloodPharma project was chosen, with additional funding being awarded by the Wellcome Trust to put together an exhibition stand. Given the financial outlay it was decided that this exhibit could be taken to other science festivals and exhibitions. Therefore, like many other projects affected by the new reliance on BIC and outreach, we see a new generation of scientists who are made to engage with the public in ways which they previously did not. Researchers who perhaps before had little inclination to engage with the public are finding it increasingly hard to avoid. Despite the push by funding bodies to do outreach, a study by Andres et al. (2005) found that a desire to contribute was considered the top motivator, followed by enjoyment and thirdly by the opportunity to develop new skills. What is evident, both

from the literature and observation of the BloodPharma team, is that scientists are being increasingly pressed by funding bodies to step outside their comfort zone and to engage with the lay public. In doing so the scientists are learning new skills about communicating their work, and its moral, ethical and social implications, to a wider audience of non-experts.

The introduction of new drugs and therapies involves not just the granting of a marketing authorisation but also an element of public willingness to accept the new therapy. In places such as the UK a decision must be made about whether a drug or therapy is acceptable to be used in NHS clinics and hospitals, based largely (but not solely) on a measure of economic factors. Indeed Jonsson et al. (2008) found that differing uptake rates of new therapies in different countries cannot be explained by health spending alone. Rather the disparities were found to reflect varying health spending priorities within different health care systems, with other factors including the incidence of specialist doctors within the population, and the reimbursement structure for prescribed medicines. Jones et al. (2001) write that the majority of decisions on implementing new therapies fell to clinicians, either at individual or at health board level. We should therefore acknowledge the autonomy that doctors have in getting new drugs (the literature is predominantly about pharmaceuticals) and therapies into clinical use, and the importance of early awareness and familiarity with a new product.

Whether this autonomy extends as far as the patient is more debatable. Whilst advertising prescription drugs has been legal in the US since 1997 (Reast, Palihawadana et al., 2004) such adverts are currently not used in the UK, and such direct-to-consumer (DTC) advertising of prescription drugs is now considered to have a significant impact on the population in countries where such advertising methods are legal (Aikin, Swasy et al., 2004). Reast et al. (2004) found that doctors in the EU were against DTC advertising as they were concerned about a rise in patient visits to doctors (which is inconsistent with the findings of Aikin et al. above) and also about undermining the doctor's role as the health care 'specialist'. The authors however did note that the internet allows patients access to a wide variety of

information and advertising from pharmaceutical companies, regardless of the restrictions imposed on print media. Such studies however have predominantly interviewed publics about such therapies out of the context of a medical scenario, and therefore I would argue are unlikely to reflect the impact that public choice has on the uptake of new therapies in the clinic (and particularly in the emergency situations in which a patient may encounter the BloodPharma product). Nevertheless such literature shows the power of consumers to push for a new drug or therapy (and the opposite in the case of GM crops).

A key driver of the BloodPharma outreach is to engage members of the public early on in the innovation of the cultured blood product. Figures often state that one in three individuals in the UK will receive a blood transfusion during their lifetime[14]. If this is correct, the origin of blood transfusion products should be of interest to most of the public. The BloodPharma team often articulated the desire that it wanted the public to be fully aware of the new product, and not to encounter the idea for the first time when they were in hospital requiring a transfusion. A focus on this early patient awareness may lead to long term benefits for the BloodPharma team, given the evidence which suggests that patient views can impact on the uptake of new therapies.

The team were also aware of the publicity which was likely to surround the project and their use of embryonic stem cells:

> *"I do think that there could be a lot of bad publicity about the embryonic source initially, which is why I think that although we need to set the paradigm using embryonic stem cells that eventually the real source might be different."* (CS/Lab)

Although views differed on the impact that this media attention may have:

[14] This 1 in 3 figure is widely repeated on internet sites, however I can find no indication of how this is calculated. Some sources say this includes both blood and platelets, others just red cell transfusions. Of more importance though is the lack of clarification over whether this is calculated per individual patient, or if it represents the total blood transfusions carried out divided by the population of that country. Personally a figure of 1 in 3 appears rather high, given that in my circle of family and friends I know of only one person who has ever received a transfusion.

> *"You know, you wonder, I mean, people read the press but it goes in one ear and out the other doesn't it? So I mean, some people go 'oh I think I heard something about that, did I read something about that?'. Yeah, that was us."* (CS/Lab)

There was however a desire to let people know about the BloodPharma project and for the scientists to be open and engaged with people outside the laboratory, presumably in an effort to overcome the mistrust in science which has often arisen from the public feeling they have been left in the dark concerning new scientific technologies. The input of the Universities and the Wellcome Trust was also in order to use this project as a demonstration of novel innovation and to publicise the excellent work being done amongst the scientific communities in the UK and Ireland.

THE NATURE OF PUBLIC OUTREACH AND THE IMPACT OF 'PUBLIC OPINION' ON THE DEVELOPMENT OF THE SCIENCE AND TECHNOLOGY

Public outreach has been an important part of the BloodPharma project and to this end the BloodPharma team has developed an interactive exhibit, consisting of a stand with interactive elements (detailed below). This exhibit has been taken to various science and career festivals, as shown in Figure 9. I am not generally comfortable with the term 'general public' and usually refer to specific 'publics'. However for ease of use I use the term here to refer to open sessions, which generally attracted lay audiences of families, children, interested parties, general passers-by etc. I have tried to make clear where specific audiences, for example schools, were targeted.

Accompanying the team to public events allowed me to take on the part of both observer and participant in the public outreach conducted by the team. Outside the scientific team I also used the BloodPharma case study when giving talks within schools as part of my role as a STEMNET[15] Ambassador. This normally takes the form of using the BloodPharma project as a case study of stem cell use, at the end of

[15] STEMNET is an organisation which allows teachers to call on help from people employed in STEM subjects (science, technology, engineering and medicine). Stem ambassadors therefore act as both a resource for schools and can engage pupils in thinking about potential careers.

a presentation on stem cell techniques and ethical considerations more widely. A list of additional outreach activities undertaken is included in Figure 13, Appendix.

Figure 9: Public outreach undertaken by the BloodPharma team

DATE	EVENT	NUMBERS ATTENDING	TARGET AUDIENCE
12/12/12	RCUK event in Westminster Parliament	Not Available	Parliamentatians and policy makers
27/10/12	Exhibit at Genova Science Festival, Italy	Not available	Researchers, schools, families, general public
23/07/12	SCRM Open Doors Event (part of wider Edinburgh Open Doors)	366	General public
30/06/12	Exhibit at Volvo Open Race (Ireland)	800,000 people passed through area where stand situated	General public
01/04/12 – 04/04/12	**Exhibit at Edinburgh Science Festival**	**689**	**General public**
10/03/12- 11/03/12	Exhibit at Newcastle Science Festival	1900	General public
03/03/12	Family Science Day, Scotland	250	General public
13/06/11	Big Bang Fair, Scotland	300	Secondary School Students
05/06/11	Glasgow University Science Festival Family Day	100	General Public
07/05/2011	Lymphoma Research Open Day, Edinburgh	91	Patients and relatives
09/04/11-22/04/11	**Edinburgh Science Festival**	**2,504**	**General public**
16/03/2011	'Let's Talk' Lecture Series, Edinburgh	101	Academics, general public, schools
10/03/11 – 12/03/11	**Big Bang Fair, London**	**2,575**	**General public and schools**
25/06/10-04/07/10	**Exhibit at Royal Soceity 350th Anniversay Exhibition, London**	**13,000 to stand, 49,946 to whole event**	**General public**

Royal Society 350th birthday festival (2010): A prestigious festival held at London's South Bank, for which the BloodPharma project was selected to be one of the exhibitors.

Big Bang Fair (2011): A science fair at the London ExCel centre, which included exhibitors from Science, Technology, Engineering, and Medicine and had a strong focus on inspiring school pupils to future careers.

Glasgow and Edinburgh Science Festivals (2011 and 2012): I did not attend the Glasgow Science Festivals, but did help at the Edinburgh Science Festivals, which were held at the National Museum of Scotland (2011) and Dynamic Earth (2012). Of note is that the Edinburgh Science Festival takes place during the school Easter holiday, impacting on the public who attend, as is discussed below.

When accompanying the team to festivals I generally possessed enough knowledge about the project to talk to members of the public about the research and the general aims and objectives of the scientific project. I was also given the role of taking photographs and asking members of the public to fill in consent forms. This allowed me to take a step back from the project and to engage in conversations about the use of stem cells, or what the attendees thought more generally about the project and the display stand. On certain occasions an attendee with more scientific knowledge required information which I did not know, and in this case I handed them over to other members of the team. Being embedded in the project as 'one of the team' (to the views of the attendees at least) gave me a unique insight into both the views of the public and also those of the BloodPharma team as they took part in such outreach.

.The exhibit which the team took to various festivals included:

- Various backboards explaining the project and giving information about stem cells more generally
- An interactive touch-screen kiosk which displayed various quizzes
- A television screen displaying rotating slides about the cultured blood project
- 'Stem Cell Stella' – a game which helped children to understand tissue differentiation using ball bearings, which they could direct down different human tissue lineages. Once they had created the 'tissue' of their choice they could then fit this into a model body.

- A table of laboratory equipment showing the flasks and containers used in stem cell culture
- Bags of 'blood' (single unit donation bags filled with food colouring and glycerol etc.) and lengths of beads which represented the number of RBCs in the width of a hair.
- Video microscope which allowed people to see the RBCs moving around the vessels under their tongue. Images were projected onto a large television screen.
- Various display stands of leaflets, free gifts of squishy RBCs, pencils, and wrist bands, all with the website address on.

This interactive exhibit allowed the BloodPharma team to promote their key messages (taken from the information sent to all demonstrators):

Figure 10: Key messages of outreach

1. We need more blood
2. We can make blood from stem cells
3. Stem cells have the potential to cure many diseases
4. (This is exciting! Not really a message, but should come across in the way we present ourselves)

These three key messages in Figure 10 have been cleverly designed by the project team to allow them to convey a lot of information in a clear format:

- We need more blood – emphasising the importance of blood donation and of donors, whilst explaining one of the main needs for the cultured blood product. This point shall be discussed in more detail in the later section on the difficulties of foresight.
- We can make blood from stem cells - introducing the BloodPharma project, its aims and project setup.
- Stem cells have the potential to cure diseases – situating the BloodPharma project within the wider stem cell field. For example explaining about research into using stem cells for stroke treatments or to overcome paralysis. Many of the attendees may have heard of projects like these and could link the use of stem cells in these projects to the BloodPharma product.

The microscope allowing attendees to see their own blood cells, along with the other props and literature, was focused on letting people know more about their own blood. The cultured blood product was then introduced as being indistinguishable from this donated blood, simply RBCs which are being made in the laboratory. This is a clear strategy for public engagement employed by the BloodPharma team, which sought to use *in vivo* donated blood as a way of capturing the attention of attendees. Most people were familiar with the shape of a RBC, or were aware of the work of the blood transfusion services, so this familiarity was used as a hook to interest people further in stem cell work. The project was very much placed as a continuum – the idea that we currently obtain RBCs from donors, but that in the future we may be able to obtain the same cells without these donors. In this way the focus was kept on the similarities between the donated blood and the cultured blood, reassuring attendees that the cultured blood would be just the same as the product that is currently used and that only the source is changing.

Throughout the outreach events with the BloodPharma team there was an overwhelmingly positive response from the attendees who came to the exhibit. During the Royal Society Event approximately 13,000 people engaged with the BloodPharma exhibit, and the team reported only one objection to the use of embryonic stem cell research (this was the only objection that I was told about in the whole of the public outreach activities). This objection was from a woman who was a Catholic and had some reservations about the destruction of embryos for research purposes. She did however admit that in an emergency medical situation she would probably accept the cultured blood product.

This perhaps reflects the types of people who came to such events, who were likely to be interested in science more broadly (given the wide range of the other exhibits on offer) and so this would have attracted fewer people with strong views than may have attended, for example, a debate specifically about embryo use in science. This is also interesting as it returns to my earlier point that many of the studies conducted with groups who object to a new technology are referring to hypothetical

circumstances, and the reality may be very different in a potentially life altering situation. The embryos used in the BloodPharma project are surplus from IVF, and many attendees were happy with this and felt that it was a positive thing that such embryos are put to good use rather than destroyed.

It must be noted that despite the large amount of outreach done by the BloodPharma team it is likely that only a certain demographic of the population was reached during such events. The events did vary in attendees, for example the Big Bang science festival had a strong careers focus and so attracted a large number of schools. The Royal Society Exhibition was held at the South Bank and so perhaps had a larger amount of 'passing trade' than the other shows, although this tended to be a mix of tourists and those already attending a show at the Royal Festival Hall. I cannot comment on the Glasgow science festivals as I did not attend these. The Edinburgh festivals were held during the Easter holidays and so did not attract school groups, instead relying on parents or carers to bring children to these events. The majority of those who came were accompanying children, and also tended to be white, middle class and well educated..

For many years public outreach was based on what has been termed the 'public deficit model', which assumed that if a public understood science then they would be more favourable towards it (Sturgis et al., 2004). This therefore led to a model of public outreach which assumed that, if a public was against a scientific innovation, that this was a failure of the scientific community to fully educate the public. Whilst writers such as Sturgis and Allum (2004) still see the value of knowledge in public attitudes towards science, it is now accepted that beliefs, and social interactions etc. also play a large part. The focus has therefore moved from giving facts to the public to a more interactive involvement between publics and scientists. This is often seen as the move from outreach to engagement, with 'outreach' implying the transfer of information from scientists to publics, and 'engagement' reflecting this more connected method of public involvement.

The distinction between outreach and engagement in the BloodPharma project became a subject of consideration for me when I presented the case study at the 2012 Science in Public Conference. During the question session one of the audience members pointed out that I had used the term 'outreach' or 'communication' during my presentation, rather than 'engagement'. The audience member seemed to be implying that as scientific communicators we no longer did 'outreach' or 'communication', and that I should have been discussing how the BloodPharma team carried out 'engagement' with the public. For me this was an opportunity to reflect on the use of these various terms to describe the transmission of scientific knowledge in large scientific projects such as the BloodPharma project.

Although the BloodPharma team have put a lot of time and effort into attending science festivals and interacting with the public it can still be argued that this has been restricted to presenting information to the public. Whilst the scientific team have entered into discussions with members of the public, this was mainly to explain the project and to answer queries from the attendees. The BloodPharma project has not yet engaged in focus groups or attempted to gather public opinion (other than on a superficial level during general conversation at exhibits). The intention thus far has therefore been to inform the public about the scientific project and its aims, and to direct the public to the additional sources of information (such as the project website). Considering the time, effort and expense which have gone into this endeavour I do not wish to imply that the BloodPharma team have been somehow lacking, indeed it has gone far beyond the public interaction of many scientific projects. I do however feel that this prompts a wider discussion about public interaction in larger scientific projects such as this.

The BloodPharma project has now secured funding of £5.4 million and, as we have seen in previous chapters, has a scientific work plan which must be considered years in advance of the actual work. This raises the question that at what point should public views be taken into account? And which voices should be listened to? It feels somewhat naïve to expect a project of this size and momentum to change their work

practices because a member of the public has objected to the use of embryos, for example. Should such projects then seek public opinion before starting?

This would return us to the earlier problem that garnering public opinion about a project that does not yet exist, and in a situation where their decision is not potential life altering, seems unlikely to yield accurate results. This point is echoed by Harmon et al. (2013) who write that attempting to engage publics during the formative scientific stage, when the social and ethical implications are not yet certain, is extremely difficult. Is the alternative option simply to not gather public opinion at all? If this project reaches clinical use then the individual can decide whether to accept the product or not. Does this option change if, in the case of something like the cultured blood product, not accepting the product could result in death? Does public opinion not matter so greatly when the technology is tucked away in a laboratory and not impacting on public lives, in stark contrast to technology such as wind turbines which gather public opinions simply due to their visibility? Perhaps the key is to move away from the engagement/communication distinction towards an appreciation of the capacity of engagement, as discussed by Parry et al. (2012). Their work using focus groups on issues related to stem cell research showed that 'engagement' had many different meanings. Whilst engagement was considered to provide an opportunity for dialogue and contribution towards decision making, the provision of education and information was also found to be important. So instead of defending the use of 'communication', perhaps I should instead acknowledge that the BloodPharma team do carry out 'engagement', albeit focused primarily on the dissemination of information.

The scientists on the BloodPharma project are aware that certain members of the community are unlikely to accept the cultured blood product, as we previously saw in Chapter Five:

> *"So yeah, Italy, Spain, most of bible belt America, there's enormous tranches of the world that wouldn't consider it still now, let alone if it's the only option, so no we're going to have to find a different source for it eventually. And also just from pure practicality that making embryonic stem cells we don't currently screen the embryos so we don't know what*

genotype they're going to have, we don't know what blood group they are." (CS/Lab)

The quote shows that the team would be willing to consider alternative methods of producing the product which would be more acceptable to the general public. However it is likely that the team will switch from embryonic stem cells to induced pluripotent stem cells due to reasons of patenting and increased screening ability, rather than primarily public opinion. Indeed throughout my data collection I saw no examples of incidences in which public opinion may shape the science and technology itself, the impact of public outreach appeared to be limited to an increased awareness amongst the scientists of potential concerns which the public may have. These concerns, however, appear to be limited to certain groups, as the quote above illustrates, and for example Jehovah's Witnesses, a small minority of the overall target market.

It would appear therefore that whilst the team have been heavily involved in public outreach there has been no discernable impact on the shaping of the technology itself. This shows that, although the nature of scientific work is changing to include a greater emphasis on engaging with the public, the outcome of this public engagement is less clear. In this case whilst public interactions may not change the technology in any way they could potentially alter the public perceptions and uptake of the cultured blood product many years down the line, but as yet it is too early to analyse the potential impact of this.

THE SCIENTIST AS PUBLIC COMMUNICATOR: THE CHALLENGE OF PERFORMING UPSTREAM ENGAGEMENT FOR A NOVEL TECHNOLOGY

The BloodPharma case study provides not only an example of a project creating public outreach opportunities but also allows observation of individual scientists as they carry out public communication. In this section I will draw on my work as a participant observer to discuss the role of the project team within these

communication events. The BloodPharma team provides an interesting case study as public events involved a large number of employees, from the Principal Investigators down to PhD students. Talking to the public was just one part of the festivals, as the scientists were involved in all aspects of the exhibitions. This included putting up and taking down stands, driving vans, crawling under tables to fix electronic equipment, administering first aid, restocking the display stands, and so forth. It was often hot, dirty and tiring, involving standing for long periods of time whilst maintaining enthusiasm for the project.

One observation that I made during the course of these outreach events is that the scientific work on the project did not, or in many cases could not, stop. At the end of a long and tiring day talking to members of the public many of the researchers went back to work. At festivals where we were close enough to go home it was not unusual for a researcher to leave Edinburgh, travel back to Glasgow to arrive at the laboratory around 9pm ready to do a few hours work feeding and maintaining their cells. They would sometimes then pop into the laboratory again before returning to Edinburgh for 10am the next morning. The cells with which these scientists work require continual feeding and maintaining, often on a daily basis, and this often requires staff members to be in the laboratory at weekends and on Christmas Day. This aspect of scientists engaging with public outreach whilst also carrying out their scientific work seems to be under discussed in the literature, perhaps due to the nature of cell culture research which requires such regular intervention. The laboratories often operate rotas of staff to undertake necessary work on the cell cultures and even when the team were away in London and unable to return to their laboratories there was a continued sense of the laboratory work still going on, of staff who had been left behind to cope with the workload of others, or people anxious to know how their experiments were working. As much as the scientific team appeared to enjoy and become enthused by the public interactions, there was still a sense that they were being taken away from the work that they should be doing.

It appears to be a common theme amongst scientists that they want to engage further with public outreach but feel unable, or unsupported in doing so. Mathews et al.

(2005) introduce a number of studies of scientists doing outreach, in which lack of time and lack of support from their employers or colleagues were cited as factors imposing on their ability to engage further with the public. Another consideration was the lack of professional recognition for public outreach, which echoes the feelings of researchers towards engaging with the regulatory system, as we saw in Chapter Five. The researchers involved in the public outreach often had little previous experience in working at science festivals or talking about their research with the lay public. Andrews et al. (2005) argue that the acquisition of new skills is one of the key motivators to becoming involved, and maintaining involvement in such activities. It is not clear if gaining new skills was a primary motivator for many of the BloodPharma team but it was apparent that they did develop considerable amounts of new knowledge during the time that they spent engaging with the public. Often one of the most difficult jobs is to distil complex research into a format which those with no scientific experience can understand. This can help researchers to focus on the important aims of their research, rather like writing an abstract forces one to pull out the primary messages from a complex study. Often at events it can be 'basic' questions asked by attendees which the scientists have no answers for. One example was that it was usual for researchers to explain that RBCs in the body are made in the bone marrow and then move out into the peripheral blood system. One attendee asked how the blood cells actually got out of the bone marrow, i.e. how they passed through the walls of the bone. Many of the researchers were stumped, and the answer had to be sought from a textbook.

In cases such as this there was a notebook located on the display stand where team members could write down questions which they had been unable to answer, along with the contact details of the attendee. This allowed the team to look up answers later and email the member of the public who had raised the question. Although this was not used very often it did help to re-enforce an important message, which is that scientists do not know everything, but that an important aspect of science is that you can go away and find out the answer. The public seemed to appreciate this honesty and the desire of the team to answer questions on a more long term basis, not just forget about them once the festival was over. It would also become apparent over the

course of a day, and especially at longer festivals, that researchers would develop a sort of 'script', a spiel which they repeated when they spoke to members of the public. This often involved a process of trial and error, for example when it became apparent that the explanation they would have liked to give was too long or complicated to engage the interest of many of the visitors. It was also interesting to observe how the demonstrators picked up bits of script from somebody else, sometimes deliberately but often unconsciously after hearing somebody repeat it time and time again.

Despite the need to explain the basic scientific work to the public it was also clear that the BloodPharma team could think on a more critical level about the ethical and social implications of their work. Many appeared to have an interest in the ethical arguments around stem cell use, and were keen to get into discussion with me about this. Many of the team had read the book about the HeLa cells (Skloot, 2010) (which had been on the best-seller lists at that time) and expressed astonishment that they had worked on this cell line themselves without knowing its provenance. Others had first hand experience of their own tissue being used without consent, and also talked of the ethical implications of using adult tissue which are often overlooked by the media and academic writers. Marks (2011) calls for more reflexivity on the part of stem cell researchers about the moral implications of their own work, and it would appear that the BloodPharma team is already engaged with such reflexive thinking.

Tait (2009) writes that, whilst the impact of public-interest groups should not be underestimated, 'upstream engagement' must necessarily result in the restriction of some scientific innovations because debate must occur before all the evidence is available. Wilsdon et al. (2004) reiterate the movement over the last 20 years from education, to participation, and now to upstream engagement as methods of increasing the publics' trust in science. The BloodPharma team is certainly carrying out upstream engagement well before the cultured blood product is expected to reach the clinic (which could be 20 years from now). Upstream engagement does, however, present a significant challenge to the BloodPharma team, due to its unique position in already having the viable alternative of blood donation.

As previously mentioned one of the core messages of the BloodPharma public outreach at events was that we simply do not have enough blood from donations. This is true in the UK, and even more pressing in other countries which do not have an established donation system. It is interesting that the team do not specifically mention the benefits of the cultured blood to certain target groups (thalassemia/sickle cell patients for example) during their outreach work. It is possible that individual demonstrators told attendees about the potential benefits to these groups, but there was no reference to target groups in either the demonstrator notes or on the project website (other than a reference to 'ensuring immune compatibility' between patient and recipient, which would also apply to the wider blood transfusion population).

In later discussions with members of the team they believed that much of the public outreach material had been written before the scientific meetings at which target groups were first identified. This is a shame as it would appear that the benefits to target groups are one of the main selling points of the cultured blood project, and would have been an ideal subject for public communication.

Unfortunately one of the other considerations of the cultured blood project is contamination of current blood donations due to Transfusion-Transmissible Infections (TTIs). Statistically the chance of infection during a blood transfusion in the UK is extremely low, but there have been highly publicised infection outbreaks in the past, and added to this is the worry that the blood transfusion services can only test for certain infections which they know are present, and for which there are tests available. For example it is possible that disease such as vCJD could be more widespread than thought, or that there may be other diseases which we do not yet know about. The ability to produce 'clean' blood is therefore a major goal of the BloodPharma project. Unfortunately this provides the team with something of a dilemma regarding public outreach. It has always been important during public engagement not to put the public off donating or accepting donated blood, as the donation system will have to supply the blood services for many years before the cultured blood product can be used. The team therefore do not want to heavily focus

on the potential for infection risk, meaning that they cannot publicise one of the main benefits of the cultured blood product.

Here we see another strategy of public outreach employed by the BloodPharma team. It prioritises certain aspects of the project when promoting to a wider audience. In this case the requirement to keep people donating and maintain trust in the current transfusion service is of primary significance, and this must be reflected in the messages used during public outreach. This balancing of a conventional therapy with the development of novel technology is perhaps a unique challenge of the BloodPharma project and may reflect more widely on the lack of public awareness about how long it takes a new therapy to be developed. It certainly represents a major challenge of carrying out upstream engagement and seeking to simultaneously promote a current technology and one which may be twenty years from clinical use.

During the promotion of the cultured blood project the team had to ensure that it did not impact in any adverse way on the attitude of the public towards both donating, and receiving donated blood. Titmuss (1997) writes that "What seemingly lags far behind the imperative demand from medical science […] is the rate of 'social growth' in the form of adequate numbers of voluntary donors". This is certainly the case in the UK, where only 4% of the population eligible to give blood do so (according to the website for the Blood Donation Service for England and North Wales, www.blood.co.uk).

Recruitment of blood donors and maintaining adequate stocks of blood is a demanding task for the UK donation services. Much has been written, especially by Titmuss, of the social 'gift' which blood donation becomes, giving to a stranger in exchange for no discernable reward. The effect of this gift was certainly evident during outreach events with the team, as many of the attendees held a strong attachment to blood donation. Many attendees were blood donors and were very proud that they were able to donate blood. Some individuals even showed us keyrings or blood donation cards, which they had received for reaching a certain number of donations. Others spoke to us of their frustration that they were not

allowed to give blood, for example because they travelled regularly, were on certain medication or had received a transfusion themselves. Although in reality the research and transfusion arms of the blood services are very separate, attendees appeared to view us as able to speak for the donation teams and give them answers to why they had been turned away.

Age was also a common factor brought up by life-long donors who had now been asked to stop giving, and were upset and disappointed that they could no longer continue donating. A couple of these previous donors said that they did not wish to stop giving as it made them feel healthier to give blood. There does not seem to be any medical justification for this, as RBCs renew constantly without blood loss, and giving blood can (among other things) adversely lower iron levels (Finch, Cook et al., 1977). It would appear that this connection between blood donation and good health goes back to the idea of blood letting which was discussed in Chapter One, continuing the thought that removing blood somehow takes away old cells and forces the body to replenish this loss with new, healthier cells. This view was voiced by a small minority however, whilst most seemed to be attached to blood donation because it gave them a chance to help others, or because they considered it something that they 'should do' for the good of society. Others had relatives who had received transfusions and felt that they should donate, given that somebody had been kind enough to do it for their family member. Quite a few people had received transfusions themselves, and were incredibly grateful for those who had given blood for them. Due to the risk of transmission of CJD a person is banned from giving blood if they have received a blood donation, anywhere in the world, since 1st Jan 1980 (UK Blood Transfusion Service, 2007). Although such people could no longer donate they had encouraged other friends and family members to become donors. Amongst the public it was clear that blood donation was an extremely emotive issue, raising considerations for the eventual public uptake of cultured blood in a society where people are incredibly attached to blood transfusion using donors.

The media can be a powerful tool in upstream engagement and the BloodPharma project has already received media attention. Whilst the team is attempting to harness

this valuable resource it can also have the problem of being difficult to control what reporters publish, opening up the possibility of inaccuracy. The BloodPharma team has focused on comparing the cultured blood product with real, *in vivo*, blood and do not wish the product to be associated with the synthetic alternatives which have previously received unsatisfactory public opinion. During outreach the team has been insistent that this product is cultured, not synthetic. Yet a quick look at the headlines of many of the articles written about the project shows that the word 'synthetic' is often used by the media. This would seem to be characteristic of the interactions between many scientists and the media, as seen in the overview by Lewenstein (1995). He writes that scientists are often very willing to engage with the media, but experience problems when the public dissemination of the research happens ahead of systematic peer review within the academic community. It will be crucial therefore in the coming years that the BloodPharma project maintains its scientific integrity, whilst still using the media as a useful tool to promote its research to a wider audience.

CONCLUSION

This chapter has revealed the main drivers and motivators behind the BloodPharma team engaging with public outreach, and has discussed how the scientists respond to their own role as public communicators. The BloodPharma team has the difficult challenge of promoting the novel technology of cultured RBC production, whilst simultaneously endorsing the current blood donation model. Their scientific method also uses embryonic stem cells, which have a history of public contention and unease. The team has therefore set out to do public outreach with many challenges, but also many benefits to harness. It has the backing of the Wellcome Trust and a large number of staff members to call upon. They also have a visually striking image, the RBC, which many people will recognise. The public are attached to blood donation and this helps to draw them in to learn more about the process of creating new blood substitutes.

We have seen that the BloodPharma project team is driven and motivated by the desire to prevent public opposition to the new cultured blood technology, as had

occurred with other advancements such as GM crops. This was considered to be especially important given the use of embryonic stem cells and the attachment that the public have to donating blood, and to receiving blood products from donors. The team also has the support of the Wellcome Trust funding to take part in outreach activities. Increased pressure from funding councils is becoming more common and outreach from larger scientific projects looks likely to become the norm, with the dual outcome of this pressure to engage with broader impact criteria often serving to force scientists into becoming more involved with public outreach. This is evident in the BloodPharma team where many of the researchers had to take part in outreach events which may not have been their natural inclination. In common with the literature, however, many of the scientists found an unknown affinity with public communication and developed new skills and insights.

Unlike many teams, who feel unsupported by their institutions to do outreach, the BloodPharma team was encouraged to take part in prestigious festivals as a way of boosting the reputation of the universities involved. There was also an understanding that they did not want the public to be faced with receiving a cultured blood product in an emergency situation, and instead wanted people to be aware of such technology well in advance of its introduction. This represented another driver to outreach, the hope that better understanding of the product by patients and doctors would lead to improved future uptake of the product.

The second section introduced the outreach work that had been done by the BloodPharma team. Specifically their focus had been on promoting the cultured blood product as similar to *in vivo* blood, whilst still retaining the links with the promise of therapies from the wider stem cell field. Another primary aim was to show how blood is used within the medical community and the need for donors to supply this demand. In doing such outreach the BloodPharma team engaged with a wide number of publics, although it is evident that many of these events attracted families who are well educated and already interested enough to bring their children to science based events.

I also questioned the main aim of such outreach in light of the literature which emphasises the move towards 'engagement' rather than 'outreach'. Whilst prioritising such two-way interaction is a heroic goal, I questioned how this is achievable with a structured scientific pathway and huge amounts of funding invested in this technology development. It seems uncertain in what context suggestions from the public could translate into a change in the product development.

As part of my data collection using participant observation I was able to talk to many of those who attended such events, and there was overwhelmingly positive support for the BloodPharma project. I was also able to see first-hand the reactions of the BloodPharma team to carrying out such outreach, with many of them enjoying the activities and benefiting from the new skills learnt. It was also apparent that what is often missing from the literature is the struggle that these researchers have between the outreach and the ongoing laboratory project. This may especially be the case for stem cell research, where the cells must be constantly looked after, resulting in either delegating to other team members or to the researchers working long hours to fit in both the outreach and their day-to-day jobs. I have addressed how the team balance the difficult task of promoting the cultured blood product without hampering donor recruitment efforts. During outreach this has been achieved by focusing on the global need for blood, whilst downplaying the infection risk which is one of the key drivers for the whole BloodPharma project. The team have focused on the 'cultured-ness' of the blood product, attempting to remove it from any links to synthetic blood products. This effort has been hampered by the media , which has often referred to the product as synthetic. This highlights the challenge that scientific projects often face between promoting scientific truths to a media that seeks to attract readers using shock or scare tactics.

In conclusion the use of participant observation has brought to my research an in-depth knowledge of the outreach and public communication done by the BloodPharma team. In many ways the feelings of the researchers about doing such outreach tally with the views of those in the literature, although the use of such observation (rather than questionnaires) has allowed me to see the reactions of the

team members, even when they are at their most tired and frustrated. It is clear that the team members have enjoyed doing such outreach, even though they may not have sought out such opportunities in the past. Whether they have been successful in promoting their product and overcoming public unease will not be clear until many years from now.

CHAPTER 7: CONCLUSION

This thesis has used an in-depth case study of the BloodPharma cultured blood project to investigate the early stage development of a novel stem cell therapy, an analysis which has enabled a prising open of the 'black box' normally surrounding the development of such therapies. This work has been about the important period of transition from an existing, well used, and publicly accepted technology to a new technology that may have huge consequences for patients and the current blood transfusion services. It is also the story of a team seeking to develop a clinical stem cell therapy in the face of uncertainty about future scale-up and regulation. In doing so this thesis has shown the changing nature of scientific work as it moves out of the laboratory space.

The goal in this case study is ambitious; to eventually replace the entire blood donation system for the UK, and perhaps the rest of the world, with the extent of scale-up and manufacturing required making this a truly paradigm-breaking scientific research project. Blood is currently donated altruistically and tested, processed, fractionated and supplied to those who need it. In the future blood may be a stem cell product that reduces reliance on blood donors and supplies a continuous source of safe, standardised blood that is cultured in the laboratory. Cultured RBCs could potentially lead to a revolutionary change in the way that blood is produced, stored and distributed, as well as bringing additional benefits to patients.

My work has investigated what an in-depth case study such as this can tell us about the development of stem cell therapies, and the hurdles and constraints which may shape and determine the innovation of new regenerative medicine based treatments. The work concentrated specifically on how scientists carried out early stage research and planned ahead for the future, and in doing so how they discussed and imagined a product that does not yet exist. The regulatory system has been analysed as an area of large uncertainty to teams developing such new innovations, and the role of public engagement introduced, with a focus on the scientific team stepping outside their area of expertise to engage with this lay audience. Whilst past research has

concentrated primarily on scientists within a laboratory situation my research has developed a more complete picture of the work and decision making involved in moving a therapy from early stage research to the clinic. This was achieved by focusing not just on laboratory observation, but by also incorporating interviews, data gathered from team meetings and teleconferences, and participant observation of public outreach events. The findings from each of the main research questions will now be discussed, before the main conclusions for this thesis are presented.

CONCLUDING THE MAIN RESEARCH QUESTIONS

How is early stage laboratory work achieved through interdisciplinary, multi-lab working, where standardisation of methods is difficult and where there exists an accepted technology?

In Chapter Three we saw that the BloodPharma team carry out interdisciplinary research under a funding model which is very different from conventional research grants and which imposes regular milestones towards which the team must aim. This brings together not just biological scientists but also clinicians, regulatory advisors and public communicators, with the recent addition of physicists and engineers. This case study has therefore followed a team doing interdisciplinary work in practice, bringing together groups with a diverse range of expertise to tackle this large research challenge.

The difficulty of standardising work across multiple laboratory sites was identified as one of the key challenges for the research teams. This difficulty of standardisation was seen to represent a key challenge of the stem cell world more broadly, where tacit knowledge plays an important role in the growth, research and maintenance of stem cell cultures. In the BloodPharma project standardisation will be crucial to achieve the future scale-up and potential automation required in order to supply the large volume requirements. Stem cell research requires a large amount of visual examination, which is dependent on the expertise and experience of the researchers. Here I have used diagrams prepared by the team as they attempt to explain such identification processes to other team members. Presentation slides are also used as an example of team members explaining their work to others in the wider team, who

work in a different disciplinary area. Tacit knowledge is seen here to be a big contributing factor towards the difficulty of standardising such research, especially of translating informal laboratory protocols into the 'locked-down' standardised protocols to be followed by the wider team.

The biological properties of the RBCs have played a central role in the early stage laboratory work, as has the team's use of the human body as an exemplar. A distinctiveness of the BloodPharma project is the presence of the already viable alternative of human blood donation, giving the team a visible target for early stage research. Using the human body as a benchmark the team have been able to mimic cues and conditions for RBC production in the laboratory. Such an examplar does raise further questions, however, about the importance of equivalence, especially the standard against which the regulatory system will measure the cultured red blood cells. As was seen in the example of foetal haemoglobin there may be an expectation to see an exact comparison between donated and cultured RBCs, even if this is not necessary for clinical function. The use of the human body as an exemplar was also considered in its relation to the natural / unnatural / synthetic distinction between cultured and donated blood. It is unclear if the language used will affect the regulation of such product, but ideas of 'matter out of place' show that the public uptake of such a product may be affected.

Informal anticipatory activities in the BloodPharma product were found to occur as the team looked ahead to the eventual end product, a process necessary to manage a consensus and carry out interdisciplinary team work. Much of this anticipation referred to an expectation of the future regulatory requirements, which included using reagents and conditions which were hoped to give the cells the best provenance. Many expectations about future regulatory requirements were not conditions articulated by the regulators themselves but an attempt by the researchers to anticipate future problems, and to tackle them at the early laboratory stage.

What does the Team see as the key challenges associated with translating cultured blood into a viable clinical product and how do these shape everyday practices?

Chapter Four saw the continuation of the work of the BloodPharma team as they considered the translation of their early stage laboratory research into a useable clinical product. We saw how the BloodPharma project can be seen as a continuation of historical work on blood donation, with the blood now moving away from human donation and into the realms of large-scale laboratory production, bringing with it the potential not only to negate the need for donors but also to produce blood in unlimited supplies.

Supplying the entire UK Blood Transfusion Service (and potentially the world's requirements) is the long term goal of the BloodPharma project, and the volumes demanded are currently unprecedented in the stem cell field. A large amount of translational work is required to move from the early stage laboratory research to a clinically acceptable product, with tacit knowledge and expertise representing one of the key challenges of future scale-up. Culture of laboratory produced RBCs still falls vastly short of the scale attained by the human body and scale-up to the numbers required to supply the UK Blood Transfusion service will demand a new industry and the development of sophisticated automation and cell sorting technologies. The BloodPharma team must anticipate future requirements and attempt to introduce scaleable protocols and develop the large bioreactors required, even when a small quantity of product cannot yet be produced in the laboratory. The team are aware of the huge translational challenge ahead and of the complex systems that will be required.

Producing enough product to be used in clinical trials represents the first scale-up target. There is still uncertainty about the nature of the clinical trials that will be required for the BloodPharma product, and this is representative of uncertainty in the wider stem cell field about the appropriateness of current clinical trial regimes (particularly concerning the use of animal models) for the testing of stem cell therapies. The BloodPharma product is considered to have an unusual risk profile

compared to other stem cell products, given that the product does not have the same DNA transfer potential, or the same longevity, as other stem cell therapies. The ReNeuron trial is therefore used as an example of a stem cell therapy which is further down the clinical trials route, and which demonstrates a more 'standard' risk profile. Data from this ReNeuron trial show the complex interactions required between trial designers, clinicians, scientists and regulators in order to develop appropriate clinical trials. Although the trial pathway for the BloodPharma product is currently unclear its unusual biological properties are likely to introduce new considerations for the regulatory bodies.

Introducing the cultured blood product in a stepping stone method allows the introduction of such blood to clinical usage, without the scale-up challenges required to supply the entire transfusion service. Target groups such as sufferers of sickle disease and thalassemia have been identified, as these patients are likely to benefit from cultured RBCs over and above the general population. Using such target groups would justify a higher initial cost for the BloodPharma product, as it could represent a significant improvement to the health and longevity of such patients. Further target markets identified include emergency patients, representing a cost saving compared to the around-the-clock infrastructure of the current blood transfusion services. Future potential changes have also been discussed by the team, such as the use of iPS cell technology, which would have advantages for biological reasons and for the patenting of the BloodPharma work.

How does the regulatory system, and perceptions of risk, shape the activities of the BloodPharma team and the development of the cultured blood product, and what can this case study tell us more generally about the regulatory system for stem cell products?

The regulatory system for stem cell research in the UK comprises a number of different regulatory bodies and has been built on a raft of existing legislation not primarily designed for stem cell derived products. The specific regulatory pathway for stem cells is still uncertain, and this uncertainty impacts on the work of the BloodPharma team. As we have previously seen, the team must attempt to anticipate

regulatory hurdles many years before these have been articulated by the regulators. The cultured blood product will be a 'test case' for the regulatory system as it will have the properties of not containing any nuclear DNA, but will also be produced and transfused in much higher quantities than most cell-based therapies. The risk profile of the product is therefore very different to other stem cell therapies.

Comparisons with the ReNeuron stroke trial have shown that navigating the regulatory system can be a costly and time-consuming process for companies, although so far the BloodPharma team appears to have encountered few major problems with the system and is maintaining a good relationship with the regulators. There are clear indications that the regulation of stem cells is a two-way process, with awareness that the scientists hold the expertise to understand the risks and benefits of their own particular research. The regulatory bodies in such a fast moving field are dependent on interactions with researchers to consider future therapies which may call for a re-evaluation of particular regulatory requirements.

Informal anticipatory activities are again a key method employed by the BloodPharma team in an attempt to plan their early stage work to anticipate future regulatory requirements, particularly concerning the long-term provenance of the cells. The scientists also use informal reasoning to draw on personal experiences or examples from the wider field in an attempt to understand the risks and complexity of stem cell regulation. The importance of expertise was a key theme in the interactions between the BloodPharma project and the stem cell regulatory system, with the BloodPharma team having an employee who deals with much of the regulatory paperwork and acts as the bridge between the regulators and the laboratory based scientists. The scientific researchers struggle to engage fully with the regulatory system which is outside their area of expertise, and this dedicated employee represents a means by which they can delegate regulatory responsibility.

The lack of expertise in regulatory affairs was suggested as a barrier for innovation by academic researchers, who may lack the advice and financial foundations necessary to navigate the regulatory pathways. There are some amongst the

BloodPharma team who are in the position of having an understanding of both the laboratory, clinical and regulatory aspects of this project. It was suggested by members of the team that knowledge of regulatory requirements is a key skill missing from the scientific community more widely, and that increased efforts should be made to equip graduates with this wider range of expertise.

What are the main drivers and motivators behind the BloodPharma team engaging with public outreach, and how do the scientists respond to their own role as public communicators?

Public outreach has constituted an important part of the BloodPharma project and the team have carried out a variety of outreach activities. The BloodPharma team has the difficult dual challenge of promoting the novel cultured RBC technology, whilst still endorsing the current donation model. The history of public unease around the use of embryonic stem cells and the attachment to human donation has motivated the BloodPharma to engage with the public at an early stage of the research.

Incidences such as GM crops have shown the importance of public acceptance of a new technology, and so the public outreach done by the BloodPharma team could be seen as a form of promotion of the new project. Such interactions between the public and scientists is becoming increasingly common as funders seek to prioritise Broader Impact Criteria. In common with many scientists most members of the BloodPharma team had not taken part in outreach activities before and found themselves developing new insights and skills through the outreach events. Although the literature reports scientists feeling unsupported in outreach, in this case the universities involved in the BloodPharma project actively encouraged public events as a way of promoting the research work. My own work as a participant observer became key to understanding the BloodPharma team's outreach work, allowing interactions both with the team itself and with the public who attended outreach events. Even in a team supported in doing outreach there was still a struggle between the public outreach work and the day-to-day laboratory work, which is perhaps specifically associated with the daily demands of stem cell cultures, and which often left scientists working long hours. A further driver was the understanding amongst

the scientists and clinicians that they wanted patients to be aware of this new technology long before clinical use, in the hope of improving future uptake.

A particular challenge of the cultured blood product is that the BloodPharma team must carry out upstream engagement whilst there is still an acceptable product in use. It is important that no promotion of the BloodPharma product should impact on the current donation system. This has led to the team focusing on the global requirements for blood whilst downplaying the reduced infection risk, which is seen as one of the key drivers for the introduction of cultured blood. Such public outreach was also an example of the scientists stepping outside their normal laboratory work and engaging with the public in an unfamiliar setting. Although for many of the scientists this represented a new area of work outside the laboratory it was apparent that many of them were very good at engaging with the public. The outreach work done by the team speaks more widely about the changing nature of scientific work, with more and more requirements for researchers to 'work' in areas outside the normal laboratory or office space.

REVIEWING THE OVERARCHING RESEARCH QUESTION

What can an in-depth case study of the BloodPharma project reveal about everyday scientific practice and the project management of a large research programme?

The BloodPharma project represents a unique case study of innovation in the field of stem cell therapies and this in-depth case study has provided an insight into the practices of an interdisciplinary team, as it seeks to carry out the early stage laboratory work and translation required to bring a new therapy from initial idea to eventual target markets.

Whilst building on previous work using laboratory studies this thesis is one of the first case studies to demonstrate the importance of 'laboratory work' moving outside the confines of the laboratory space. Here we see scientists engaging with the areas of regulation, innovation and public acceptance, and doing so in an interlinked way – with these concerns not just shaping the laboratory work but the laboratory work also

impacting on future regulation, target markets and public outreach. A common theme is the increasing requirements for scientists to move outside their primary area of expertise and engage with the translation of therapies into clinical usage. Rather than the traditional view of the researcher shut away in the laboratory we see an appreciation that scientific work is about more than laboratory experiments. This does not simply mean that researchers are moving from the bench to the office and the ever increasing demands of computer based analysis, rather that they are moving into other areas outside the traditional research space.

The requirement for laboratory workers to engage with the regulatory system is another example of scientists moving outside the laboratory, where scientists are increasingly finding that they are required to gain expertise in understanding the regulatory implications of their projects. This expertise is by no means trivial, with many of the researchers articulating that they do not have the time or background knowledge to engage fully with the regulatory documents. The findings presented here regarding the importance of expertise in the regulatory arena highlight the changing nature of laboratory work, and promote an increased awareness of the importance of scientists engaging with the regulatory documents. The BloodPharma team have been able to delegate this responsibility to a dedicated member of staff, but it is becoming apparent that younger researchers will be increasingly required to develop knowledge of the regulatory factors surrounding their research.

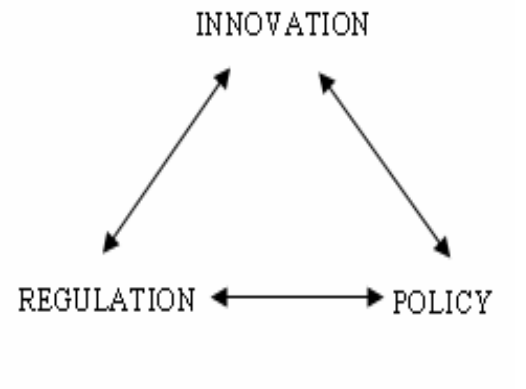
For many of the BloodPharma team the use of public engagement represented another area of work with which they had to engage, and many found new or previously undeveloped skill sets in dealing with the public and in explaining their work to those outside the research sphere. The input of the Wellcome Trust and Edinburgh and Glasgow Universities in supporting such outreach mirrors a wider trend amongst research councils to encourage scientists to move out of the laboratories. What can be seen from the BloodPharma case study is that, in addition to requiring new skill sets, public outreach requires a large time commitment and financial investment. As a consequence of the outreach work some members of the team also sought extra outreach opportunities, for example by becoming

ambassadors for STEMNET. This demonstrates that an appreciation of the role of public outreach, and the opportunity to carry this out in a supported way, has the potential to be developed by a scientist throughout their career. As interactions with lay audiences become increasingly required in large research projects the skills developed here will hopefully be of increased use to such scientists in the future. EuroStemCell (an organisation supplying information and educational resources about stem cells) have already expressed interest in the findings of this thesis and the lessons which can be learnt from the BloodPharma public outreach activities, particularly the unusual position of the team as a dual promoter of both a novel and an existing technology.

This thesis is an in-depth case study of a 'beyond-lab' project, a study of scientific work moving outside the laboratory space. The BloodPharma project is an example of a scientific team engaging with a research, innovation and public outreach triangle in a way which emphasises the importance of this scientific work which takes place outside the laboratory. The triangle often includes the influence of policy on the translation of innovations to new therapies, and whilst it is a little early in the developmental pathway for policy to have been directly considered in relation to the cultured blood product, we can consider the use of public outreach as the first stages of engaging with public and policy influences outside the scientific community. The BloodPharma project represents a study in which the regulatory, innovation and public spheres have been considered as important influences since the inception of the project. In this way the project team has the opportunity to engage in two-way dialogue with the regulators and future policy makers, not simply being constrained by regulations but by having the opportunity to present the cultured blood project as a technology worthy of future regulatory discussion. The findings from this thesis should therefore act as an example of good working amongst an interdisciplinary team, who recognise the importance of all three points on the innovation triangle and seeks to build it into its everyday work. This is not to say that the BloodPharma project is an example of 'perfect' interdisciplinary work, however this case study acts as an example of a team carrying out an extremely ambitious project. As large research projects start to become increasingly popular lessons, both good and bad,

can be learnt from the BloodPharma team, with the aim of developing a smoother translation pathway for future stem cell therapies.

Figure 11: Innovation/Regulation/Policy triangle



The Innovation/Regulation/Policy triangle helps to explain the interlinked nature of translation for new bioscience innovations.
This triangle is used to explain the outside influences which can impact on the development of new innovations, although the three corners of the triangle are sometimes labelled differently, for example 'business' rather than 'innovation'.

The use of interdisciplinary working and expectations highlight the hurdles to be faced in the translation of such a large project into a clinically based stem cell therapy. Only the future will tell if the scale-up, regulatory and research streams of the project come together successfully to produce a cultured blood product for target markets, and eventually for the entire population.

SUGGESTIONS FOR FURTHER WORK

The findings from this in-depth case study of the BloodPharma project have shed new light on the innovation of a novel stem cell therapy and the potential challenges for translation, and these findings can contribute to further work in the area.

Public acceptance for the project has so far been gathered through broad reaching outreach activities, however there is scope for a more detailed analysis of specific target groups. This would include patient groups such as thalassemia or sickle cell anaemia sufferers, who are expected to be the first target markets for the cultured blood product. Dialogue with these groups would provide further understanding of potential concerns about the BloodPharma product. These concerns could then be fed into further public outreach work in an effort to make the wider public more aware of

the cultured blood product, and to attempt to allay concerns. Such a project is already being undertaken by myself, with other researchers at the ESRC Innogen Centre, as part of the continued funding for the BloodPharma project which is being supplied by the Scottish Funding Council. The natural/unnatural/synthetic distinction discussed in this thesis has already been highlight by the BloodPharma team as an important area of research to carry forward, in the context of the wording used to explain this cultured blood technology to the wider public.

The use of tacit knowledge within stem cell work has been discussed in previous literature but this case study has contributed some practical examples of teams working to standardise work across different laboratory spaces. More work could be done gathering examples of standardisation methods from other projects, such as the use of pictures given in this thesis to help the researchers differentiate different types of cells. This could also be augmented by looking at incidences where standardisation has either worked well, or failed, and assessing how the expertise of the researchers has contributed to this. One example from the BloodPharma project would be the student who mistakenly identified mould patches as balls of cells.

The BloodPharma project represents a niche case study within stem cell research and has contributed to a wider understanding of the field because it highlights exceptional considerations and risk profiles. The use of the ReNeuron study as an example of a stem cell therapy slightly further down the regulatory pathway has also allowed a view of what may be in store for the future of the BloodPharma project. As more therapies start to be developed there will be the ability to add more case studies to this project, and also to revisit the BloodPharma project further down the line. This will allow us to see whether the speculation of the researchers about future regulatory concerns came true, and how the regulators responded to the unique risk profile of this cultured blood project.

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APPENDIX

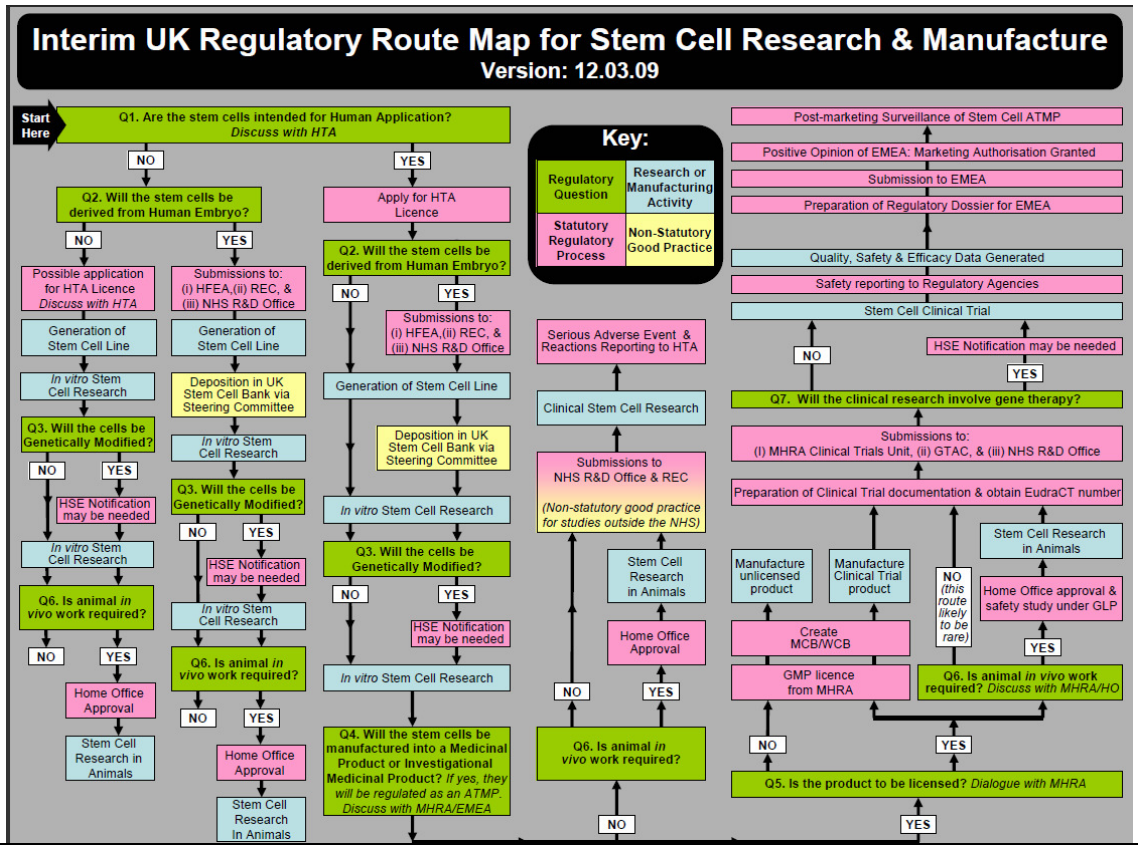

Figure 12: Interim regulatory route map for stem cell research and manufacture
Showing the complexity of the regulatory system in the UK. This version of the map has now been replaced by an interactive toolkit, available at http://www.sc-toolkit.ac.uk

Figure 13: Additional outreach work Detailing some of my additional outreach work in my role as an Ambassador for STEMNET	
01/11/11	Spoke about the cultured blood 'Vampires and Vegetarianism in the 21st Century' at the ESRC festival of social science.
March 2011	Took part in 'I'm a Scientist Get Me Out of Here' in the Stem Cells section.
29/01/11	Internal SSU seminar on the history of blood transfusion and its development into a stem cell derived product.
Autumn 2010/Spring 2011	Assisted a 6th form student doing a Baccalaureate project on public reactions to embryonic stem cell use.
04/11/10	I went to speak to a small group of medicinal students at the University of Edinburgh about ethics of stem cells as part of a wiki based project on stem cell therapies.
02/11/10	Organised a lesson for a local school about stem cell research, ethics, regulation and the BloodPharma project, along with one of the lab based post-docs.
Other:	A career day with a school in Edinburgh, and helped at a 'Dance your Genome' workshop